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Fusarium graminearum Schwabe is one of the most prevalent diseases of wheat (Triticum
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quantitative and more than 100 quantitative trait loci (QTL) have been described. Two
well-validated and highly reproducible QTL, Fhb1 and Qfhs.ifa-5A have been widely
investigated, but to date the underlying genes have not been identified. We have
investigated a gene co-expression network activated in response to F. graminearum using
RNA-seq data from near-isogenic lines, harboring either the resistant or the
susceptible allele for Fhb1 and Qfhs.ifa-5A. The network identified pathogen-responsive
modules, which were enriched for differentially expressed genes between genotypes or
different time points after inoculation with the pathogen. Central gene analysis
identified transcripts associated with either QTL within the network. Moreover, we
present a detailed gene expression analysis of four gene families (glucanases, NBS-LRR,
WRKY transcription factors and UDP-glycosyltransferases), which take prominent roles in
the pathogen response. A combination of a network-driven approach and differential gene
expression analysis identified genes and pathways associated with Fhb1 and Qfhs.ifa-5A.
We find G-protein coupled receptor kinases and biosynthesis genes for jasmonate and
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3.774-2.94.993 0 1.589.2 2.065.397.199.518.477 1.867.557 2.424l-.755.159zm-9.971-
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.4.1.8-.5.7-.5 0-.7-.1-.9-.6-.3-1.3-2.9-2.3-4-1.6-.2.1-.2.4-.2.6 0 1.7 0 3.4.1 5.2 0
.9.6 1.5 1.5 1.5h2.1c3.1 0 4.1-.8 4.9-3.8.1-.6.3-.8.9-.7.7 0 .5.5.5.9 0 1.4-.1 2.9-.1
4.3 0 .7-.3.9-1 .9-2.3-.1-4.7-.1-7.1-.1zm-94.6-3.7v2.7c0 .3.2.8-.4.8-.4 0-.9.1-1-.5
0-.2-.2-.4-.3-.6-.3-.7-.5-1-1.2-.3-2.6 2.4-5.6 2.6-8.7 1.3-3.3-1.3-5.3-3.8-5.7-7.3-.9-
6.6 3.6-11.5 10.1-11.2 1.6.1 3.1.6 4.4 1.7.5.4.8.4.9-.3.1-.5.3-1 1-.8.8.1.5.8.5 1.2.1
1.5.1 3.1.1 4.6 0 .3.3.9-.4 1-.6.1-.9-.2-1-.8-.4-1.4-1.1-2.6-2.1-3.5-3.2-2.8-7.4-1.7-
8.7 2.4-.8 2.7-.8 5.5.1 8.2 1.5 4.3 6 5.2 9 1.8.9-.9 1.5-2 1.8-3.2.2-.6.6-.6 1-.6.6 0
.4.5.4.8.2.8.2 1.7.2 2.6z"/><path d="M34.7 37.8V.7c0-.4.1-.7.5-.7s.5.3.6.7V75c0
.4-.1.8-.6.7-.4 0-.5-.3-.5-.7V37.8zm70.6 2.4v37.4c0
.3-.2.5-.5.5s-.5-.2-.5-.5V3.2c0-.4.2-.8.6-.7.4 0 .5.4.5.7v1c-.1 11.9-.1 23.9-.1
36zM69.5 50.7V13.6c0-.4.2-.7.6-.6.3 0 .5.3.5.6v74.6c0 .3-.2.5-.5.6-.4
0-.6-.3-.6-.6V50.7zM0 51.9V14.7c0-.3.2-.5.5-.5s.5.2.6.5v74.7c0 .3-.2.5-.6.5-.3
0-.5-.3-.5-.6V51.9zm140 0v37.5c0 .3-.2.4-.5.4s-.5-.1-.5-.4c-.1-.4-.1-.7-.1-
1.1V14.6c0-.3.2-.5.6-.5.3 0 .5.2.5.5v37.3z"/><path class="st0" d="M53.3 36.3c9.3-.2 12
8.4 9.4 13.8-1.8 3.6-5.8 5.7-10.5 5.3-7.2-.7-11.2-7.6-8.1-14 1.6-3.2 4.9-5.1 9.2-5.1zm-
5.1 13.9c.9 2.4 2.7 3.6 5.3 3.6 2.5 0 4.2-1.2 5.1-3.6.9-2.5.9-5.1.3-7.7-.7-3.1-2.6-4.6-
5.6-4.6-3 0-4.8 1.6-5.5 4.7-.2 1.1-.3 2.1-.3 3.5 0 1.2.1 2.7.7 4.1zm37.3-13.7c2.1-.1
4.2-.2 6.3.1 3.1.5 4.7 2.4 4.6 5.3-.1 2-1.2 3.5-3.5 4.2-1.8.6-3.6.7-5.4.6-.8 0-1.1.2-1
1 .1 1.3.1 2.6 0 3.9-.1 1.3.6 2 1.9 2.1.5 0 .9 0 .9.7 0 .8-.6.6-1 .6h-7.4c-.5 0-.9.1-
1-.6 0-.7.5-.7.9-.7 1.3-.1 1.8-.8 1.7-2.1V40c0-1.4-.5-2.1-1.9-2.2-.4 0-.8 0-.8-.6
0-.7.4-.7.9-.7h4.8zm1 6c.1.9-.4 2.3.2 2.6 1 .6 2.3.2 3.5-.2 1.4-.5 2-1.4 2-3.3 0-
1.4-.3-2.7-1.8-3.3-1-.4-2.1-.5-3.1-.5-.6 0-.8.2-.8.8v3.9z"/></symbol><symbol id="icon-
crossref" viewBox="0 0 140 70"><path d="M0 47.53V33.18l11.76-3.85 20.86 7.14z"/><path
d="M20.79 18.34L0 25.48l11.76 3.85 20.86-7.14z"/><path d="M11.76 29.33l20.86-
7.14v14.28zM32.62.14v14.28l-11.83 3.92L0 11.13z"/><path d="M20.79 18.34L0
25.48V11.13zM82.32 62.3h.84v.77h-.84v-.77zm0 1.4h.84v3.71h-.84V63.7zm1.33-
1.4h4.13v.77h-1.61v4.34h-.91v-4.34h-1.61v-.77zm4.69 0h.84v1.89c.21-.35.63-.56

1.12-.56.77 0 1.33.42 1.33 1.26v2.52h-.84V65.1c0-.56-.21-.84-.7-.84-.56
0-.91.42-.91.98v2.17h-.84V62.3zm4.55 3.43c0 .56.28 1.12.98 1.12.49 0
.77-.21.91-.63h.77c-.21.77-.84 1.26-1.68 1.26-1.12 0-1.82-.77-1.82-1.96 0-1.05.7-1.96
1.75-1.96 1.19 0 1.89 1.05 1.75 2.17h-
2.66zm1.89-.56c0-.49-.35-.98-.91-.98s-.98.42-.98.98h1.89zm1.4-
1.47h.77v.56c.21-.42.63-.63 1.12-.63.77 0 1.33.42 1.33
1.26v2.52h-.84V65.1c0-.56-.21-.84-.7-.84-.56 0-.91.42-.91.98v2.17h-.84V63.7h.07zm3.64
0h.63v-1.12h.84v1.12h.7v.63h-.7v1.96c0 .35 0 .49.42.49h.35v.63c-.21 0-.35.07-.56.07-.84
0-.98-.35-1.05-.91V64.4h-.63v-.7zm2.8-1.4h.84v.77h-.84v-.77zm0
1.4h.84v3.71h-.84V63.7zm4.13 1.19a.831.831 0 00-.84-.7c-.42 0-.98.21-.98 1.33 0 .63.28
1.26.98 1.26.49 0 .77-.28.91-.84h.84c-.14.98-.77 1.47-1.68 1.47-1.12 0-1.82-.84-1.82-
1.89 0-1.12.63-1.96 1.82-1.96.84 0 1.61.42 1.68 1.33h-.91zm4.55 1.68c0
.21.07.28.21.28h.21v.56c-.14.07-.35.07-.49.07-.35 0-.56-.14-.63-.42-.35.28-.84.42-
1.26.42-.63 0-1.26-.35-1.26-1.05 0-.91.7-1.05 1.4-1.12.56-.14 1.12-.07
1.12-.49s-.42-.49-.77-.49c-.49 0-.77.21-.84.56h-.84c.07-.98.84-1.19 1.68-1.19.7 0
1.47.28 1.47 1.05v1.82zm-.77-1.05c-.28.14-.63.14-.98.21-.35.07-.63.21-.63.63 0
.35.49.49.77.49.35 0 .91-.21.91-.7v-.63h-.07zm1.33-1.82h.63v-
1.12h.84v1.12h.7v.63h-.7v1.96c0 .35 0 .49.42.49h.35v.63c-.21 0-.35.07-.56.07-.84
0-.98-.35-1.05-.91V64.4h-.63v-.7zm3.22 2.03c0 .56.28 1.12.98 1.12.49 0
.77-.21.91-.63h.77c-.21.77-.84 1.26-1.68 1.26-1.12 0-1.82-.77-1.82-1.96 0-1.05.7-1.96
1.75-1.96 1.19 0 1.89 1.05 1.75 2.17h-
2.66zm1.89-.56c0-.49-.35-.98-.91-.98s-.98.42-.98.98h1.89zm-69.65-15.4c-.21-1.47-1.12-
2.03-2.52-2.03-1.12 0-2.24.42-2.24 1.75 0 1.26 1.61 1.4 3.22 1.82 1.61.35 3.22.91 3.22
2.87 0 2.17-2.1 3.01-3.92 3.01-2.24 0-4.13-1.12-4.13-3.57h1.26c0 1.68 1.4 2.45 2.94
2.45 1.19 0 2.52-.35 2.52-1.82 0-1.4-1.61-1.61-3.22-1.96-1.61-.35-3.22-.84-3.22-2.66 0-
2.03 1.82-2.94 3.64-2.94 2.03 0 3.64.98 3.71 3.15h-1.26v-.07zm4.27-1.47H50.4v-
1.47h1.19v1.47zm-1.19 1.26h1.19v7.28H50.4v-7.28zm2.66 0h1.12v1.05c.56-.84 1.33-1.26
2.38-1.26.91 0 1.68.35 2.03 1.26.49-.77 1.33-1.26 2.31-1.26 1.47 0 2.45.63 2.45
2.1v5.32h-1.19v-4.76c0-.91-.21-1.61-1.4-1.61s-1.89.7-1.89 1.89v4.55h-1.19v-
4.76c0-.91-.28-1.61-1.4-1.61-1.4 0-1.96 1.33-1.96 1.89v4.55h-1.19v-7.35h-.07zm12.95-
1.26h-1.19v-1.47h1.19v1.47zm-1.19 1.26h1.19v7.28h-1.19v-7.28zm2.87-2.73h1.19v10.08h-
1.19V46.83zm9.24 10.01c-.21.14-.49.21-.84.21-.63 0-.98-.35-.98-1.12-.63.77-1.54 1.12-
2.59 1.12-1.33 0-2.38-.56-2.38-2.03 0-1.68 1.26-2.03 2.45-2.24 1.33-.28 2.45-.14 2.45-
1.05 0-1.05-.84-1.19-1.61-1.19-.98 0-1.75.28-1.82 1.4h-1.19c.07-1.82 1.47-2.45 3.08-
2.45 1.33 0 2.73.28 2.73 2.03v3.78c0 .56 0 .84.35.84.07 0 .21 0 .35-.07v.77zm-1.89-
3.71c-.49.35-1.4.35-2.17.49s-1.47.42-1.47 1.33c0 .77.7 1.05 1.4 1.05 1.61 0 2.24-.98
2.24-1.68v-1.19zm3.01-3.57h1.12v1.54c.56-1.19 1.4-1.75 2.66-1.68v1.26c-1.96 0-2.66
1.12-2.66 2.94v3.22h-1.19v-7.28h.07zM84 48.3h-1.19v-1.47H84v1.47zm-1.19 1.26H84v7.28h-
1.19v-7.28zm4.76 0h1.47v1.05h-1.47v4.55c0 .56.14.63.91.63h.56v1.05h-.91c-1.26 0-
1.75-.28-1.75-1.61v-4.62h-1.26v-1.05h1.26v-2.17h1.19v2.17zm5.6 8.26c-.56 1.4-1.05 1.96-
2.1 1.96-.28 0-.56 0-.84-.14v-1.12c.21.07.49.14.7.14.49 0 .77-.21.98-.63l.49-1.26-2.87-
7.21h1.33l2.1 5.95 2.03-5.95h1.26l-3.08 8.26zm15.4-7.98c-.28-1.4-1.4-2.17-2.8-2.17-2.38
0-3.43 1.96-3.43 4.06 0 2.31.98 4.2 3.43 4.2 1.75 0 2.8-1.26 2.87-2.87h1.33c-.28 2.52-
1.82 4.06-4.34 4.06-3.15 0-4.62-2.31-4.62-5.25s1.68-5.32 4.76-5.32c2.1 0 3.85 1.12 4.13
3.29h-1.33zm2.73-3.01h1.19v3.85c.42-.84 1.4-1.26 2.31-1.26 1.89 0 2.52 1.12 2.52
2.66v4.76h-1.19v-4.9c0-.91-.56-1.47-1.47-1.47-1.47-1.47 0-2.17.98-2.17 2.31v4.13h-
1.19V46.83zm13.65 7.77c-.35 1.61-1.47 2.45-3.08 2.45-2.31 0-3.43-1.61-3.5-3.85 0-2.17
1.47-3.78 3.43-3.78 2.59 0 3.36 2.38 3.29 4.2h-5.46c-.07 1.26.7 2.38 2.24 2.38.98 0
1.68-.49 1.89-1.4h1.19zm-1.19-2.03c-.07-1.12-.91-2.03-2.1-2.03-1.26 0-2.03.91-2.1
2.03h4.2zm7.49-.63c-.21-.91-.84-1.47-1.82-1.47-1.75 0-2.24 1.4-2.24 2.87 0 1.33.63 2.66
2.1 2.66 1.12 0 1.82-.7 2.03-1.75h1.26c-.28 1.75-1.4 2.8-3.22 2.8-2.24 0-3.43-1.54-
3.43-3.71s1.12-3.92 3.43-3.92c1.68 0 2.94.77 3.15 2.52h-1.26zm2.31-5.11h1.19v5.95l3.29-
3.15h1.61l-2.87 2.66 3.08 4.62h-1.54l-2.52-3.78-1.12 1.05v2.73h-1.19V46.83h.07zM53.27
26.25c-.28-1.82-2.03-3.22-4.06-3.22-3.64 0-5.04 3.08-5.04 6.37 0 3.08 1.4 6.16 5.04
6.16 2.52 0 3.92-1.68 4.2-4.13h3.99c-.42 4.62-3.57 7.56-8.12 7.56-5.74 0-9.1-4.27-9.1-
9.59 0-5.46 3.36-9.8 9.1-9.8 4.06 0 7.49 2.38 7.98 6.65h-3.99zm5.53-
1.05h3.5v2.52h.07c.7-1.68 2.52-2.87 4.27-2.87.28 0 .56.07.77.14v3.43c-.35-.07-.91-.14-
1.33-.14-2.73 0-3.64 1.96-3.64 4.27v6.02H58.8V25.2zm15.61-.42c4.2 0 6.93 2.8 6.93 7.07
0 4.27-2.73 7.07-6.93 7.07-4.2 0-6.93-2.8-6.93-7.07.07-4.27 2.73-7.07 6.93-7.07zm0
11.41c2.52 0 3.29-2.17 3.29-4.27 0-2.17-.77-4.27-3.29-4.27s-3.22 2.17-3.22 4.27c0
2.1.77 4.27 3.22 4.27zm11.27-1.96c0 1.61 1.4 2.24 2.8 2.24 1.05 0 2.38-.42 2.38-1.68 0-
1.12-1.54-1.47-4.2-2.1-2.1-.49-4.27-1.19-4.27-3.57 0-3.43 2.94-4.27 5.81-4.27 2.94 0
5.6.98 5.88 4.27h-3.5c-.07-1.4-1.19-1.82-2.52-1.82-.84 0-2.03.14-2.03 1.26 0 1.33 2.1
1.47 4.2 2.03 2.17.49 4.27 1.26 4.27 3.78 0 3.5-3.08 4.69-6.09 4.69-3.08 0-6.16-1.19-
6.3-4.69h3.57v-.14zm13.44 0c0 1.61 1.4 2.24 2.8 2.24 1.05 0 2.38-.42 2.38-1.68 0-1.12-
1.54-1.47-4.2-2.1-2.1-.49-4.27-1.19-4.27-3.57 0-3.43 2.94-4.27 5.81-4.27 2.94 0 5.6.98
5.88 4.27h-3.5c-.07-1.4-1.19-1.82-2.52-1.82-.84 0-2.03.14-2.03 1.26 0 1.33 2.1 1.47 4.2
2.03 2.17.49 4.27 1.26 4.27 3.78 0 3.5-3.08 4.69-6.09 4.69-3.08 0-6.16-1.19-6.3-
4.69h3.57v-.14zm10.08-9.03h3.5v2.52h.07c.7-1.68 2.52-2.87 4.27-2.87.28 0

.56.07.77.14v3.43c-.35-.07-.91-.14-1.33-.14-2.73 0-3.64 1.96-3.64 4.27v6.02h-
3.64V25.2zm12.67 7.56c.07 2.31 1.26 3.43 3.29 3.43 1.47 0 2.66-.91 2.87-1.75h3.22c-1.05
3.15-3.22 4.48-6.3 4.48-4.2 0-6.86-2.87-6.86-7.07 0-3.99 2.8-7.07 6.86-7.07 4.55 0 6.79
3.85 6.51 7.98h-9.59zm5.95-2.31c-.35-1.89-1.12-2.87-2.94-2.87-2.31 0-3.01 1.82-3.08
2.87h6.02zm5.74-2.8h-2.17V25.2h2.17v-1.05c0-2.38 1.47-4.06 4.48-4.06.63 0 1.33.07
1.96.07v2.73c-.42-.07-.91-.07-1.33-.07-.98 0-1.4.42-1.4 1.54v.84h2.52v2.45h-
2.59v10.92h-3.71V27.65h.07zM41.3 62.3h2.24c1.47 0 1.75.91 1.75 1.54s-.28 1.54-1.75
1.54h-1.33v1.96h-.91V62.3zm.91 2.38h1.33c.42 0 .91-.21.91-.84 0-.7-.42-.84-.84-.84h-
1.33v1.68h-.07zm3.36.84c0-1.12.7-1.96 1.82-1.96 1.19 0 1.82.84 1.82 1.96s-.7 1.96-1.82
1.96c-1.19 0-1.82-.84-1.82-1.96zm2.87 0c0-.63-.35-1.26-1.05-1.26-.7 0-1.05.63-1.05
1.26s.35 1.33 1.05 1.33c.7 0 1.05-.7 1.05-1.33zm.98-1.82h.84l.7 2.73.7-2.73h.84l.63
2.73.77-2.73h.84l-1.12 3.64h-.84l-.7-2.73-.7 2.73h-.84l-1.12-3.64zm6.37 2.03c0 .56.28
1.05.98 1.05.49 0 .77-.21.91-.63h.77c-.21.77-.84 1.26-1.68 1.26-1.12 0-1.82-.77-1.82-
1.96 0-1.05.7-1.96 1.75-1.96 1.12 0 1.89 1.05 1.75 2.17h-
2.66v.07zm1.89-.49c0-.49-.35-.98-.91-.98s-.91.42-.98.98h1.89zm1.54-
1.54h.77v.7c.07-.42.56-.84 1.05-.84h.28v.84c-.14 0-.21-.07-.35-.07-.56 0-.98.42-.98
1.26v1.75h-.84V63.7h.07zm3.08 2.03c0 .56.28 1.05.98 1.05.49 0
.77-.21.91-.63h.77c-.21.77-.84 1.26-1.68 1.26-1.12 0-1.82-.77-1.82-1.96 0-1.05.7-1.96
1.75-1.96 1.12 0 1.89 1.05 1.75
2.17H62.3v.07zm1.89-.49c0-.49-.35-.98-.91-.98s-.91.42-.98.98h1.89zm4.97
2.1h-.77v-.49c-.21.42-.7.56-1.12.56-1.12 0-1.68-.84-1.68-1.96 0-1.33.77-1.89 1.61-
1.89.49 0 .98.14 1.19.56V62.3h.84v5.04h-.07zm-1.82-.49c.7 0 1.05-.63 1.05-1.33
0-.84-.42-1.26-.98-1.26-.77 0-1.05.7-1.05 1.33 0 .63.28 1.26.98 1.26zm4.83-
4.55h.84v1.89c.21-.35.7-.56 1.12-.56 1.12 0 1.68.91 1.68 1.96 0 .98-.49 1.89-1.61
1.89-.49 0-1.05-.14-1.26-.63v.49h-.77V62.3zm1.75 1.96c-.7 0-1.05.49-1.05 1.33 0 .77.35
1.26 1.05 1.26.77 0 .98-.63.98-1.26.07-.7-.28-1.33-.98-1.33zm2.1-.56h.91l.98 2.73.91-
2.73h.84l-1.4 3.85c-.28.63-.42 1.26-1.33 1.26-.21 0-.35 0-.56-.07v-.7c.14 0
.28.07.35.07.35 0 .49-.21.56-.49l.07-.28-1.33-3.64z"/></symbol><symbol id="icon-humana-
press-logo" viewBox="0 0 160 30"><path d="M54.32 13.137v6.864c0 1.303.074 1.379 1.227
1.535v.653c-1.153.23-2.226.46-3.222.844v-1.536c-.501.424-1.958 1.497-3.071 1.497-1.728
0-2.802-1.187-2.802-2.955l-.003-3.562c0-1.496-.113-1.691-1.382-1.845v-.652c1.191-.228
2.351-.495 3.31-.839l.003 6.211c0 1.38.643 2.221 1.794 2.221.731 0 1.574-.535 2.151-
1.072l-.005-4.024c0-1.496-.115-1.691-1.382-1.845v-.652c1.188-.228 2.422-.497
3.382-.843zm87.251.037c.932 0 1.504.189 1.973.381.211.467.463 1.885.506
2.332l-.613.191c-.508-1.294-1.209-2.141-2.225-2.141-.656 0-1.535.509-1.535 1.273 0
.739.756 1.33 1.795 1.774 1.675.721 3.088 1.38 3.088 2.95 0 2.056-2.012 3.072-3.77
3.072-1.105 0-2.186-.402-2.586-.722-.148-.338-.342-1.8-.342-2.732l.594-.064c.447 1.357
1.422 2.733 2.691 2.733.721 0 1.641-.529 1.641-1.269 0-.722-.525-1.296-1.756-1.889-
1.08-.509-3.002-1.225-3.002-2.985 0-1.59 1.401-2.904 3.541-2.904zm8.057 0c.934 0
1.506.189 1.973.381.211.467.466 1.885.507 2.332l-.615.191c-.51-1.294-1.203-2.141-2.221-
2.141-.66 0-1.537.509-1.537 1.273 0 .739.758 1.33 1.797 1.774 1.674.721 3.088 1.38
3.088 2.95 0 2.056-2.016 3.072-3.773 3.072-1.104 0-2.184-.402-
2.586-.722-.147-.338-.338-1.8-.338-2.732l.592-.064c.445 1.357 1.42 2.733 2.691
2.733.721 0 1.643-.529 1.643-1.269 0-.722-.528-1.296-1.758-1.889-1.078-.509-3.002-
1.225-3.002-2.985 0-1.59 1.4-2.904 3.539-2.904zm-16.766-.004c1.883 0 3.379 1.612 3.379
3.415 0 .578-.08.809-.539.885-.344.037-2.99.228-5.41.307.075 2.495 1.572 3.568 3.07
3.568.844 0 1.457-.231 2.225-.998l.498.691c-1.266 1.572-2.762 1.958-3.451 1.958-2.725
0-4.301-2.074-4.301-4.529 0-2.953 2.266-5.297 4.529-5.297zm-32.588.012c.775 0 1.404.189
1.927.615.861.655 1.05 1.545 1.05 2.713v3.647c0 .977.333 1.25.689 1.25.249 0
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1.132-.125.487.027.469-.35.469-.484 0-1.153-.467-1.153-.997
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1.927.615.856.655 1.047 1.545 1.047 2.713v3.647c0 .977.336 1.25.69 1.25.253 0
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0-.36.252-.615.69-.954.733-.508 2.159-1.272 3.353-1.505zm35.319-4.841c1.695 0 2.961.246
3.852.87l.712 1.578 1.778 1.578 3.249 0 2.939-2.202 4.378-4.494
4.644-.336.043-.544.043-.813.043l-1.171-.28v2.99c0 1.891.198 2.025 2.135 2.18v.772h-
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1.892.179 2.003 1.914 2.158v.772h-6.11v-.772c1.764-.15 1.99-.28 2.002-1.977l.001-
4.373h-6.798v4.192c0 1.869.177 2.003 1.892 2.158v.772h-5.95v-.772c1.613-.15 1.853-.259
1.867-1.975l.001-8.79c0-1.89-.199-2.003-1.958-2.159v-.772h5.973zm52.499
4.798v1.534c.5-.421 1.958-1.497 3.071-1.497 1.726 0 2.802 1.19 2.802 2.955v4.453c0
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2.041.507 0 1.027-.2 1.428-.507.2-.213.294-.52.294-1.041v-2.935c0-1.121-.093-
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0 .707-.093.093.093.093.414 0 .507-.707.107-1.721.32-2.335.614-.093
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.2.093.2.093 0 .294-.093.707-.093 1.521v3.162l.093.002zm8.965-2.642c0-.707 0-.907.2-
1.027.2-.2.707-.294 1.227-.294 1.734 0 2.748 1.428 2.748 3.255 0 1.521-.614 2.949-2.335
2.949-.614 0-1.027-.2-1.321-.614-.307-.4-.414-.907-.414-1.521v-2.748h-.105zm-1.32
3.656v1.521c0 .093.093.093.2.093h.093c.093-.08.2-.294.414-.294.093 0
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3.456-3.362-3.456-.907 0-1.628.294-2.041.614-.093 0-.2-.093-.2-.414v-3.255c0-.814 0-
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1.027 0-1.121-.507-1.521l-.2-.093c-.093-.093-.093-.294 0-.294.414-.093 1.321-.414
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1.121 0-.814-.707-1.227-1.321-1.628-1.027-.614-1.734-1.227-1.734-2.135 0-1.321 1.027-
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0 .2.093 0 .507-.093 1.428-.093 2.228v3.776c0 .2 0 .294.093.294.614-.507 1.521-.907
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1.121-.507-1.935-1.734-1.935-.614 0-1.027.2-1.428.507-.295.294-.415.414-.415
1.028v2.949c0 1.321 0 1.428.707 1.521l.414.093c.093.093.093.414 0 .414-.507 0-
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0-.414l.414-.093c.614-.093.707-.294.707-1.521v-8.139h-.348zm9.339 4.883c0-.707
0-.814-.507-1.121l-.2-.093c-.093-.093-.093-.294 0-.294.414-.093 1.428-.614
1.841-.907.093 0 .2 0 .2.093 0 .614-.093 1.521-.093 2.228v3.162c0 1.321 0 1.428.707
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0-.814-.507-1.121l-.2-.093c-.093-.093-.093-.294 0-.294.414-.093 1.428-.614
1.734-.907.093 0 .2 0 .2.093v.814c0 .093.093.2.2.2.707-.507 1.628-.907 2.442-.907 1.521
0 2.041 1.027 2.041 2.228v3.042c0 1.321 0 1.428.707 1.521l.414.093c.093.093.093.414 0
.414-.507 0-1.027-.093-1.628-.093-.614 0-1.227 0-1.628.093-.093-.093-.2-.294
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1.628.093-.093-.093-.2-.294 0-.414l.414-.093c.614-.093.707-.294.707-1.521v-
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1.628 0-2.855 1.121-2.855 2.642a2.35 2.35 0 001.321 2.135c0
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1.321 1.428.2.093 0 .294-.093.414l-1.228 1.226c-.094.094-.2.414-.2.614 0 .907.814 2.041
2.949 2.041 2.335 0 4.483-1.428 4.483-3.362 0-1.734-1.521-1.935-2.442-1.935-.814 0-
1.521.093-2.135.093-.814 0-1.227-.294-1.227-.707 0-.507.614-.814.814-1.027.2 0
.507.093.814.093 2.228 0 2.949-1.628 2.949-2.842v-.907h1.321c.294 0

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2.949 2.041 2.335 0 4.483-1.428 4.483-3.362 0-1.734-1.521-1.935-2.442-1.935-.814 0-
1.521.093-2.135.093-.814 0-1.227-.294-1.227-.707 0-.507.614-.814.814-1.027.2 0
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0 1.027-.2 1.428-.507.2-.2.294-.507.294-1.027v-2.949c0-1.121-.093-1.227-.614-
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1.121 0 2.041.093.093-.093.2-.414 0-.414l-.707-.093c-.614-.093-.707-.2-.707-1.521v-
1.828c0-.414.093-.507.2-.507.2 0 .614.093 1.027.093 2.548 0 4.363-1.734 4.363-4.269 0-
1.841-1.121-3.255-2.949-3.255-1.121 0-2.228.707-2.442.814-.093 0-.2-.093-.2-.2 0-.2
0-.507.093-.814 0-.093-.093-.093-.2-.093-.507.294-1.321.814-1.734.907-.093.093-.093.2 0
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4.59v.212c.002.237 0 .55-.048.958-.09.745-.378 1.526-.734
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1.505-.325-.013-.536-.016-.829-.084-.645-.07-1.198-.222-1.7-.495.16-.416.279-.776.41-
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.03-.01.015-.025.012.028.045-.006.109-.012.181-.026.313-.06.82-.132.976-.22 1.297-.786
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0-.333-.026-.633 0-.893.03-.306-.026-.642-.013-.94.004-.07-.002-.042
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.013.973-.151 2.137-.064 2.843.313zm8.94-.313c.338.07.681.132.976.265.772.349 1.394.854
1.806 1.518.038.032.036.027.073.06.366.678.618 1.292.674 2.277l.006.008.003-.008c0
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1.552-.662.257-.072.618-.078.784-.145.619-.05 1.438-.106 2.012.013zm29.14-.073c1.66.073
2.96.913 3.626 2.084.147.323.321.65.409 1.072.245.759.205 1.709.205 2.842 0 .736.043
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9.113.12.204.224.303.373.435.662.603 1.68.469 2.433-.1.561-.254 1.09-.566
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.588-.312.88-.19.447-.379 1.11-.566
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57.944-.661 1.955-1 2.844-.582.028-1.215.004-1.818.013-.169-.411-.3-.882-.471-
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1.416-3.153 3.787-3.153h3.406V13.46c0-1.73-.897-2.502-2.909-2.502-1.405 0-2.15.326-
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1.291-.522.727-.735 1.602-.735 3.02s.213 2.293.735 3.019c.593.844 1.502 1.291 2.626
1.291 1.046 0 1.72-.325 2.559-1.241l1.022.982c-1.1 1.172-2.043 1.59-3.581 1.59-3.005 0-
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2.628l-.013.083c-.041.25-.055.497-.073.7.323.05.554.061.855.083.015.025 0
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28.708c-.414.12-.713.205-.942.257l.004.011c-.447.13-.907.193-1.365.193M2.39
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1.227-1.175.614 0 1.343.204 2.292.641l.945-1.885c-1.097-.64-2.222-.95-3.438-.95-2.36 0-
3.769 1.265-3.769 3.385 0 2.118 1.649 2.936 2.972 3.594.961.477 1.79.889 1.79 1.665 0
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1.206-2.82 3.344-2.82.712 0 1.48.192 2.247.465.055.575.111 1.233.137
2.383l-.576.026c-.273-.958-.712-2.134-2.111-2.134-1.04 0-1.562.71-1.562 1.56 0 2.601
4.77 2.053 4.77 5.451.002 1.617-1.452 3.012-3.59 3.012m7.813-.107c2.055-.248 3.7-1.811
3.7-4.109 0-1.424-.96-2.903-2.658-2.903-.192 0-.384.026-.578.136l-1.479.768v-
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1.643c-.659 0-.905-.303-.905-.55 0-.245.274-.629.602-.737.191 0 .413.027.496.027 1.369
0 2.877-.903 2.877-2.577 0-.464-.166-1.066-.386-
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3.532 4.029-5.614h-1.59c-.768.273-1.918 1.972-1.918 2.957H2.468l1.027-.82-.658.544-
1.755-2.025S0 18.097 0 18.014s.027-.136.027-.136l2.769-3.752.494-1.479.74-.273.769-
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1.454-.201-1.855-.351v4.711c0 1.705.201 1.855 2.506 2.055v.952h-7.067v-.952c1.805-.2
1.955-.351 1.955-2.055V19.279c0-1.754-.05-1.805-1.754-1.955v-.852c1.503-.3 2.907-.752
4.36-1.253v1.904l2.707-1.403c.351-.2.702-.25 1.052-.25 3.108 0 4.862 2.706 4.862
5.313.001 4.21-3.006 7.067-6.766 7.518zm.652-10.977c-.802 0-1.854.552-
2.506.953v7.418c.552.602 1.454 1.053 2.557 1.053 1.454 0 3.358-1.103 3.358-4.862-.001-
3.159-1.505-4.562-3.409-4.562zm15.638 1.253c-.3-.401-.702-.501-1.203-.501-.651 0-
1.454.752-2.005 2.306v4.662c0 1.704.201 1.855 2.356 2.005v1.002h-6.817v-1.002c1.705-.15
1.905-.301 1.905-2.005V19.38c0-1.705-.15-1.705-1.705-2.005v-.852c1.504-.301 2.958-.602
4.26-1.103v3.007h.05c.902-1.654 2.156-2.957 3.308-2.957 1.003 0 1.705.751 1.705
1.554.001 1.152-1.202 2.155-1.854 1.553zm9.574 9.473h-6.416v-1.002c1.704-.15 1.955-.301
1.955-2.105v-5.414c0-1.955-.15-1.955-1.805-2.155v-.852c1.554-.301 3.107-.652 4.36-
1.103v9.523c0 1.804.15 1.955 1.905 2.105v1.003zm-3.308-15.287a1.69 1.69 0 01-1.704-
1.705c0-1.002.752-1.754 1.704-1.754 1.003 0 1.754.752 1.754 1.754 0 .953-.752 1.705-
1.754 1.705zm18.646 15.287h-5.915v-1.002c1.403-.15 1.604-.301 1.604-1.905v-4.912c0-
1.805-.802-2.908-2.306-2.908-.953 0-2.055.702-2.807 1.403v6.416c0 1.604.151 1.755 1.554
1.905v1.002h-6.115v-1.002c1.704-.15 1.955-.301 1.955-1.905v-5.764c0-1.705-.1-1.805-
1.604-2.005v-.852c1.504-.301 2.908-.602 4.21-1.103v2.005c.652-.551 2.556-1.955 4.01-
1.955 2.255 0 3.659 1.554 3.659 3.859v5.814c0 1.604.25 1.755 1.755 1.905v1.004zm14.284-
11.929c-.2.451-.751 1.303-1.203 1.554l-1.454-.15c.401.551.702 1.654.702 2.506 0 3.058-
2.756 4.712-5.263 4.712-.15 0-.551-.05-.902-.05-.602.2-1.103.902-1.103 1.353s.451 1.003
1.654 1.003h3.007c1.754 0 4.11.852 4.11 3.659 0 3.208-3.358 5.914-7.268 5.914-3.409 0-
5.213-2.104-5.213-3.809 0-1.103.551-1.955 2.907-3.759-.853-.301-2.356-1.153-2.256-2.757
1.153-.501 2.206-1.403 2.656-1.955-1.353-.452-2.606-2.055-2.606-3.859 0-3.258 2.907-
5.012 5.313-5.012 1.052 0 2.055.25 2.907.702 1.303-.05 2.606-.201 3.81-.351l.202.299zm-
3.959 13.433c-.702-.251-1.654-.301-3.208-.301-2.155 0-3.108 1.604-3.108 2.808 0 1.704
1.504 3.007 3.759 3.007 2.506 0 3.91-1.654 3.91-3.308 0-1.053-.601-1.905-1.353-2.206zm-
3.208-12.882c-1.052 0-2.256 1.103-2.256 3.208s1.103 3.609 2.607 3.609c1.102 0
2.155-.953 2.155-3.258.001-1.955-.952-3.559-2.506-3.559zm17.693 4.411c-.451.05-
3.909.301-7.067.401.1 3.308 2.055 4.711 4.01 4.711 1.102 0 1.904-.3 2.907-
1.303l.652.902c-1.654 2.055-3.609 2.556-4.511 2.556-3.559 0-5.614-2.707-5.614-5.914 0-
3.91 2.958-6.967 5.915-6.967 2.456 0 4.411 2.105 4.411 4.461-.001.752-.151 1.053-.703
1.153zm-4.26-4.36c-1.152 0-2.356 1.253-2.656 3.408l4.311-.1c.551 0 .651-.15.651-.651 0-
1.355-.952-2.657-2.306-2.657zm14.435 1.854a1.71 1.71 0 00-1.203-.501c-.651 0-1.504.752-
2.055 2.306v4.662c0 1.704.2 1.855 2.355 2.005v1.002h-6.867v-1.002c1.754-.15 1.905-.301
1.905-2.005V19.38c0-1.705-.1-1.705-1.704-2.005v-.852c1.604-.301 3.007-.602 4.311-
1.103v3.007h.049c.852-1.654 2.105-2.957 3.309-2.957.952 0 1.704.751 1.704 1.554.001
1.152-1.252 2.155-1.804 1.553zm6.53.752c0-6.065 3.357-9.323 7.568-9.323 4.16 0 7.317
3.208 7.317 9.022 0 6.366-3.609 9.323-7.568 9.323-4.059 0-7.317-3.158-7.317-
9.022zm1.353 0c0 3.759 2.005 7.919 6.015 7.919h.051c4.061 0 6.015-4.061 6.015-8.17 0-
3.608-1.755-7.97-6.015-7.97-4.262 0-6.066 4.211-6.066 8.221zm18.196 6.967v6.716h-
1.403V19.629c0-1.704-.051-2.857-.101-3.91h1.303l.101 2.056c.952-1.604 2.405-2.306 4.21-
2.306 3.008 0 5.163 2.406 5.163 6.266 0 4.46-2.606 6.566-5.464 6.566-1.654 0-
3.057-.752-3.809-2.005zm.1-6.667c-.05.351-.1.702-.1 1.053v2.607c0 .3 0 .651.1.952.501
2.005 2.056 2.958 3.659 2.958 2.707 0 4.11-2.306 4.11-5.414 0-2.707-1.354-5.263-4.061-
5.263-1.653 0-3.257 1.353-3.708 3.107zm12.584 2.056c.049 4.16 2.153 5.463 4.511 5.463

1.554 0 2.455-.3 3.207-.702l.301 1.053c-.601.351-1.854.752-3.71.752-3.559 0-5.663-2.606-5.663-6.165 0-4.061 2.256-6.616 5.413-6.616 3.859 0 4.611 3.559 4.611 5.413 0 .301 0 .551-.05.802h-8.62zm.098-1.053h7.168c0-2.055-.952-4.11-3.407-4.11-2.407 0-3.562.205-3.761 4.11zm19.198 7.418v-7.468c0-2.105-.752-3.96-3.157-3.96a3.537 3.537 0 00-3.409 2.657c-.099.301-.149.702-.149 1.103v7.669h-1.403v-9.373c0-1.204-.051-1.905-.101-2.958h1.303l.05 1.955c.702-1.253 2.206-2.205 4.011-2.205 1.403 0 4.21.702 4.21 4.861v7.719h-1.355z"/></symbol><symbol id="icon-alert" viewBox="0 0 18 18"><path fill-rule="evenodd" d="M4 10h2.5a.5.5 0 010 1H3.414l-1.121 1.121a1 1 0 00-.293.707V13h14v-.172a1 1 0 00-.293-.707L14 10.414V7A5 5 0 004 7zm3 4a2 2 0 104 0zm-5 0a1 1 0 01-1-1v-.172a2 2 0 01.586-1.414L3 10V7a6 6 0 1112 0v3l1.414 1.414A2 2 0 0117 12.828V13a1 1 0 01-1 1h-4a3 3 0 01-6 0z"/></symbol><symbol id="icon-arrow-left-bullet" viewBox="0 0 8 16"><path d="M3 8l5 5v3L0 8l8-8v3L3 8z"/></symbol><symbol id="icon-arrow-left" viewBox="0 0 16 16"><path d="M7.002 15.002a1 1 0 102 0V3.386l2.482 2.482a.994.994 0 001.403.02 1.001 1.001 0 00.001-1.416l-.001-.001L8.71 1.295a1 1 0 00-1.415 0h-.001L3.118 4.472a.99.99 0 00-.016 1.4 1 1 0 001.414.003l.006-.006 2.48-2.482v11.615z"/></symbol><symbol id="icon-book" viewBox="0 0 18 18"><path fill-rule="evenodd" d="M4 13V2h1v11h11V2H3a1 1 0 00-1 1v10.268A1.99 1.99 0 013 13zm12 1H3a1 1 0 000 2h13zm0 3H3a2 2 0 01-2-2V3a2 2 0 012-2h13a1 1 0 011 1v14a1 1 0 01-1 1z"/></symbol><symbol id="icon-chevron-down" viewBox="0 0 16 16"><path d="M8 8.586l3.293-3.293a1 1 0 011.414 1.414l-4 4a1 1 0 01-1.414 0l-4-4a1 1 0 011.414-1.414z" fill-rule="evenodd"/></symbol><symbol id="icon-chevron-right" viewBox="0 0 16 16"><path d="M7.782 7L5.3 4.518a.994.994 0 01-.02-1.403 1.001 1.001 0 011.417 0l4.176 4.177a1.001 1.001 0 010 1.416l-4.176 4.177a.991.991 0 01-1.4.016 1 1 0 01.003-1.42L7.782 9l1.013-.998z" fill-rule="evenodd"/></symbol><symbol id="icon-chevron-up" viewBox="0 0 16 16"><path d="M8 7.414l3.293 3.293a1 1 0 001.414-1.414l-4-4a1 1 0 00-1.414 0l-4 4a1 1 0 001.414 1.414z" fill-rule="evenodd"/></symbol><symbol id="icon-collections" viewBox="3 3 32 32"><path fill-rule="evenodd" d="M25.583 30.125V7.121c0-.013-.003-.017.003-.017l-19.482.002v23.03c0 .97.79 1.76 1.76 1.76h18.193a3.525 3.525 0 01-.474-1.771zm-21.25.01V7.106c0-.984.792-1.772 1.769-1.772h19.484c.976 0 1.768.8 1.768 1.788v5.296h5.313V30.11c0 1.96-1.581 3.557-3.531 3.557H7.864a3.533 3.533 0 01-3.53-3.531zm23.021-15.948v15.938a1.77 1.77 0 103.542 0V14.187h-3.542zM9.646 10.646h12.396v7.083H9.646v-7.083zm1.77 1.77v3.542h8.855v-3.541h-8.854zM9.647 19.5h12.396v1.77H9.646V19.5zm0 3.542h12.396v1.77H9.646v-1.77zm0 3.541h12.396v1.771H9.646v-1.77z"/></symbol><symbol id="icon-download-rounded"><path d="M0 13c0-.556.449-1 1.002-1h9.996a.999.999 0 110 2H1.002A1.006 1.006 0 010 13zM7 1v6.8l2.482-2.482c.392-.392 1.022-.4 1.403-.02a1.001 1.001 0 010 1.417l-4.177 4.177a1.001 1.001 0 01-1.416 0L1.115 6.715a.991.991 0 01-.016-1.4 1 1 0 011.42.003L5 7.8V1c0-.55.444-.996 1-.996.552 0 1 .445 1 .996z"/></symbol><symbol id="icon-download" viewBox="-301 390 9 14"><path d="M-301 395.6l4.5 5.1 4.5-5.1h-3V390h-3v5.6h-3zm0 6.5h9v1.9h-9z"/></symbol><symbol id="icon-editors" viewBox="0 0 18 18"><path fill-rule="evenodd" d="M8.726 2.546A3 3 0 105.37 7.519l.63.409v1.024l-.79.329A5.221 5.221 0 002 14.099V15H1v-.901a6.221 6.221 0 013.825-5.741 4 4 0 114.976-6.213 4.965 4.965 0 00-1.075.4zM6 17H5v-.901a6.221 6.221 0 013.825-5.741 4 4 0 114.349 0A6.221 6.221 0 0117 16.099V17h-1v-.901a5.221 5.221 0 00-3.21-4.818l-.79-.33V9.929l.63-.409a3 3 0 10-3.260l.63.409v1.024l-.79.329A5.221 5.221 0 006 16.099z"/></symbol><symbol id="icon-ethics"><path d="M12.182 2.272l1.038-1.038a4.014 4.014 0 015.677 0l1.038 1.038a3.21 3.21 0 002.271.941h2.684a4.014 4.014 0 014.014 4.014v2.684c0 .852.339 1.669.94 2.271l1.039 1.038a4.014 4.014 0 010 5.677l-1.038 1.038a3.211 3.211 0 00-.94 2.271v2.684a4.014 4.014 0 01-4.015 4.014h-2.684c-.852 0-1.669.339-2.27.94l-1.039 1.039a4.014 4.014 0 01-5.677 0l-1.038-1.038a3.211 3.211 0 00-2.27-.94H7.226a4.014 4.014 0 01-4.014-4.015v-2.684c0-.852-.338-1.669-.94-2.27l-1.039-1.039a4.014 4.014 0 010-5.677l1.038-1.038a3.208 3.208 0 00.941-2.27V7.226a4.014 4.014 0 014.014-4.014H9.91c.852 0 1.669-.338 2.271-.94zm1.136 1.136a4.817 4.817 0 01-3.407 1.41H7.227a2.409 2.409 0 00-2.408 2.41V9.91a4.817 4.817 0 01-1.411 3.407L2.37 14.356a2.41 2.41 0 000 3.406L3.408 18.8a4.817 4.817 0 011.41 3.406v2.684a2.409 2.409 0 002.41 2.409H9.91a4.82 4.82 0 013.407 1.41l1.038 1.038c.94.941 2.465.941 3.406 0L18.8 28.71a4.817 4.817 0 013.406-1.41h2.684a2.409 2.409 0 002.409-2.409v-2.684c0-1.278.507-2.503 1.41-3.406l1.038-1.038a2.408 2.408 0 000-3.406l-1.038-1.038A4.817 4.817 0 0127.3 9.91V7.227a2.409 2.409 0 00-2.41-2.407h-2.684A4.817 4.817 0 0118.8 3.408L17.762 2.37a2.409 2.409 0 00-3.406 0l-1.038 1.038zM15.03 17.86l4.332-4.73a.803.803 0 111.224 1.04l-4.844 5.367a.803.803 0 01-1.112.076l-3.1-2.605a.803.803 0 011.027-1.233l2.473 2.085zm1.028 7.832c-.41 0-.41-1.482 0-1.482a8.152 8.152 0 006.657-12.858.741.741 0 111.21-.857 9.634 9.634 0 01-7.867 15.197zM21.68 8.234a.741.741 0 01-.866 1.203 8.152 8.152 0 00-12.908 6.578.741.741 0 01-1.483-.007A9.635 9.635 0 0121.68 8.234zM6.907 19.077a.741.741 0 011.407-.464 8.155 8.155 0 007.745 5.598.741.741 0 110 1.482 9.637 9.637 0 01-9.152-6.616z"/></symbol><symbol id="icon-explore"><path d="M15 28.3c7.3 0 13.3-6 13.3-13.3S22.3 1.7 15 1.7 1.7 7.7 1.7 15s6 13.3 13.3 13.3zm0 1.7C6.7 30 0 23.3 0 15S6.7 0 15 0s15 6.7 15 15-6.7 15-15 15zm0-4.2c-.5 0-.8-.3-.8-.8s.3-.8.8-.8c5 0 9-4 9.2-8.8 0-.5.3-.8.8-.8s.8.3.8.8c-.1 5.8-

5 10.4-10.8 10.4zm-.5-21.6c.5 0 .8.3.8.8s-.3.8-.6.8c-5 .2-8.9 4.4-8.9 9.2 0 .5-.3.8-.8.8s-.8-.3-.8-.8c0-5.8 4.5-10.5 10.3-10.8zm1.8 13.5l-2-2c-.3-.3-.3-.8 0-1.2.3-.3.8-.3 1.2 0l2 2 2.7-6.7-7.5 2.8-3 7.5 6.6-2.4zm6.9-10.9L18.7 18c-.2.5-.5.8-1 1L6.5 23.5 11 12.3c.3-.7.7-1 1.2-1.2l11-4.3z"/></symbol><symbol id="icon-ext-link" viewBox="0 0 16 16"><path d="M12.9 16H3.1C1.4 16 0 14.6 0 12.9V3.2C0 1.4 1.4 0 3.1 0h3.7v1H3.1C2 1 1 2 1 3.2v9.7C1 14 2 15 3.1 15h9.7c1.2 0 2.1-1 2.1-2.1V8.7h1v4.2c.1 1.7-1.3 3.1-3 3.1z"/><path d="M12.8 2.5l.7.7-9 8.9-.7-.7 9-8.9z"/><path d="M9.7 0L16 6.2V0z"/></symbol><symbol id="icon-info-bordered" viewBox="470.812 270.868 18 18"><path d="M479.812 270.868c-4.972 0-9 4.029-9 9s4.028 9 9 9c4.971 0 9-4.029 9-9s-4.029-9-9-9zm0 16.875a7.875 7.875 0 01-7.875-7.875 7.875 7.875 0 1115.75 0 7.875 7.875 0 01-7.875 7.875z"/><path d="M479.284 279.586c.089-.238-.024-.361-.13-.361-.489 0-1.123 1.16-1.359 1.16-.093 0-.173-.092-.173-.174 0-.238.581-.801.751-.971.526-.506 1.217-.895 1.979-.895.567 0 1.174.346.703 1.639l-.952 2.604c-.079.199-.224.531-.224.746 0 .092.054.186.159.186.395 0 1.121-1.135 1.304-1.135.067 0 .158.086.158.199 0 .385-1.542 2.043-2.874 2.043-.477 0-.804-.225-.804-.732 0-.641.447-1.734.538-1.963l.924-2.346zm.727-3.41c0-.586.498-1.066 1.082-1.066.527 0 .91.357.91.906 0 .615-.501 1.068-1.098 1.068-.541-.002-.894-.361-.894-.908z"/></symbol><symbol id="icon-opr" viewBox="0 0 18 18"><path d="M.9 2.5c-.2-.2-.4-.3-.6-.2-.3.2-.3.4-.3.6 0 .8 0 1.7.1 2.5 0 .5.3.7.7.6.9 0 1.7-.2 2.5-.3h.2c.5-.2.6-.5.3-.8-.2-.2-.4-.4-.6-.5-.1-.1-.2-.2-.4-.3.5-.6 1-1.1 1.7-1.5 4.6-3 10.9-.5 12 4.9.9 4.4-2.2 8.6-6.7 9.2-3.7.5-7.2-1.6-8.4-5.1 0-.1-.1-.2-.1-.3-.1-.3-.5-.5-.5-.8-.4-.3.1-.5.4-.4.8.4 1.3 1.1 2.4 2 3.4 1.4 1.5 3.1 2.4 5.1 2.8 3 .5 5.6-.2 7.8-2.2 2.1-1.9 3-4.2 3-6.9-.1-4-3.1-7.6-7.1-8.4-3.3-.9-6.2 0-8.6 2.3-.2.1-.3.3-.5.5-.3-.2-.6-.5-.9-.7z"/><path d="M13 4.7c-2.6 1.6-4.5 3.6-5.3 4.6L5.6 7.7l-.9.7L8.3 12c.6-1.6 2.6-4.6 4.9-6.8l-.2-.5z"/></symbol><symbol id="icon-remove" viewBox="-296 388 18 18"><path d="M-291.7 396.1h9v2h-9z"/><path d="M-287 405.5c-4.7 0-8.5-3.8-8.5-8.5s3.8-8.5 8.5-8.5 8.5 3.8 8.5 8.5-3.8 8.5-8.5 8.5zm0-16c-4.1 0-7.5 3.4-7.5 7.5s3.4 7.5 7.5 7.5 7.5-3.4 7.5-7.5-3.4-7.5-7.5-7.5z"/></symbol><symbol id="icon-rss"><ellipse cx="3.305" cy="20.702" rx="3.306" ry="3.298"/><path d="M15.978 24h-4.684c0-6.224-5.057-11.27-11.294-11.27V8.058c8.824 0 15.978 7.137 15.978 15.942z"/><path d="M19.2 23.95C19.2 13.366 10.604 4.79 0 4.79V0c13.255 0 24 10.723 24 23.95h-4.8z"/></symbol><symbol id="icon-search"><path d="M13.545 12.648a.641.641 0 01.006.903.646.646 0 01-.903-.006l-2.664-2.663a6.125 6.125 0 11.897-.898l2.664 2.664zm-7.42-1.273a5.25 5.25 0 100-10.5 5.25 5.25 0 000 10.5z"/></symbol><symbol id="icon-springer-arrow-left"><path d="M15 7a1 1 0 000-2H3.385l2.482-2.482a.994.994 0 00.02-1.403 1.001 1.001 0 00-1.417 0L.294 5.292a1.001 1.001 0 000 1.416l4.176 4.177a.991.991 0 001.4.016 1 1 0 00-.003-1.42L3.385 7H15z"/></symbol><symbol id="icon-springer-arrow-right"><path d="M1 7a1 1 0 010-2h11.615l-2.482-2.482a.994.994 0 01-.02-1.403 1.001 1.001 0 011.417 0l4.176 4.177a1.001 1.001 0 010 1.416l-4.176 4.177a.991.991 0 01-1.4.016 1 1 0 01.003-1.42L12.615 7H1z"/></symbol><symbol id="icon-springer-info" viewBox="0 0 24 24"><path d="M12 0c6.627 0 12 5.373 12 12s-5.373 12-12 12S0 18.627 0 12 5.373 0 12 0zm.554 9.1h-1a1 1 0 00-1 1v8a1 1 0 001 1h1a1 1 0 001-1v-8a1 1 0 00-1-1zM12 5c-.464 0-.847.146-1.148.44-.301.292-.452.675-.452 1.15 0 .474.15.86.452 1.16.3.3.684.45 1.148.45.477 0 .863-.15 1.158-.45.295-.3.442-.686.442-1.16 0-.475-.147-.858-.442-1.15C12.863 5.145 12.477 5 12 5z"/></symbol><symbol id="icon-springer-tick-circle" viewBox="0 0 24 24"><path d="M12 24C5.373 24 0 18.627 0 12S5.373 0 12 0s12 5.373 12 12-5.373 12-12 12zM7.657 10.79a.991.991 0 00-1.423.133 1.06 1.06 0 00.13 1.464l3.897 3.367a1 1 0 001.405-.097l6.093-6.944a1.06 1.06 0 00-.115-1.465.991.991 0 00-1.424.12l-5.452 6.121-3.111-2.699z"/></symbol><symbol id="icon-updates" viewBox="0 0 18 18"><path d="M16.98 3.484h-.48c-2.52-.058-5.04 1.161-7.44 2.903-2.46-1.8-4.74-2.903-8.04-2.903-.3 0-.54.29-.54.58v9.813c0 .29.24.523.54.581 2.76.348 4.86 1.045 7.62 2.903.24.116.54.116.72 0 2.76-1.858 4.86-2.555 7.62-2.903.3-.058.54-.29.54-.58V4.064c0-.29-.24-.523-.54-.581zm-15.3 1.22c2.34 0 4.86 1.509 6.72 2.786v8.478c-2.34-1.394-4.38-2.09-6.72-2.439V4.703zm14.58 8.767c-2.34.348-4.38 1.045-6.72 2.439V7.374C12 5.632 14.1 4.645 16.26 4.645v8.826z"/><path d="M9 .058c-1.560-2.76 1.22-2.76 2.671C6.24 4.181 7.5 5.4 9 5.4c1.5 0 2.76-1.22 2.76-2.671 0-1.452-1.2-2.67-2.76-2.67zm0 4.413c-.96 0-1.8-.755-1.8-1.742C7.2 1.8 7.98.987 9 .987s1.8.755 1.8 1.742c0 .93-.84 1.742-1.8 1.742z"/></symbol><symbol id="icon-logo-springer-greyscale" viewBox="0 0 112 30"><path d="M23.651 23.02H4.27v-1.191h1.643c.287-3.86 3.982-5.297 6.036-8.417H9.568c-1.15.411-2.875 2.956-2.875 4.434H3.696l1.041-1.232-.986.821-2.628-3.038S0 14.233 0 14.11s.041-.206.041-.206l4.147-5.625.739-2.217 1.109-.41 1.15-1.601-.411-2.794c1.108-.411 2.176-.041 2.71.492A14.315 14.315 0 009.444.025c1.971-.205 2.668.862 2.997 2.053a13.98 13.98 0 011.478.206.669.669 0 01.616-.452c.369 0 .616.287.616.616v.164c.863.287 1.684.698 2.423 1.15a.585.585 0 01.492-.247c.37 0 .616.287.616.616 0 .164-.041.287-.123.37.698.575 1.273 1.273 1.807 2.012a.76.76 0 01.287-.082c.369 0 .657.287.657.616 0 .247-.123.452-.328.534.411.739.739 1.56.985 2.422.041-.041.123-.041.164-.041.369 0 .616.287.616.616s-.205.575-.451.616c.164.862.287 1.725.369 2.628.369 0 .657.287.657.616 0 .369-.287.615-.616.657 0 .862-.041 1.807-.123 2.71.328.041.575.328.575.657s-.287.616-.657.616h-.041c-.164.903-.328 1.806-.534

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2.956L9.198 4.05c0-1.027-.452-1.437-1.067-1.725l.287 2.012-.699 1.027.329.944-
2.176.739-.616 1.766-3.819 5.256 1.438 1.724 1.601-1.355.369.246v2.012h.862c.37-1.437
1.56-3.121 2.669-3.942l-.616-.739.903-.78.862 1.068s3.08 0 3.08-.041c.452-.985.739-
2.176.739-3.572h1.191c0 4.681-2.34 6.529-5.256 9.403-1.068 1.067-2.012 2.217-2.135
3.777zM3.573 12.796c.041.534-.041 1.355-.329 1.766l-.862-.329c.287-.41.452-.985.452-
1.478zm4.721-4.558l-1.847.985-.124-1.519 1.93-.206zm15.357 20.859H4.27v-
2.382h19.381zm12.528-5.749c-1.56 0-2.792-.37-3.983-.903-.246-1.068-.329-2.505-.411-
3.983l.945-.164c.534 2.012 1.273 3.983 3.736 3.983 1.725 0 2.751-1.068 2.751-2.669 0-
4.229-7.021-3.284-7.021-8.171 0-2.217 1.807-4.229 5.01-4.229 1.068 0 2.217.287
3.367.698.082.862.164 1.848.205 3.573l-.862.041c-.411-1.438-1.067-3.203-3.162-3.203-
1.56 0-2.341 1.068-2.341 2.341 0 3.901 7.145 3.08 7.145 8.171 0 2.421-2.177 4.515-5.379
4.515zm11.702-.164c-.657-.041-1.191-.164-1.519-.287v3.859c0 1.396.164 1.52 2.053
1.684v.78h-5.789v-.78c1.478-.164 1.601-.287 1.601-1.684V15.793c0-1.437-.041-1.478-
1.437-1.601v-.698c1.232-.246 2.381-.616 3.572-1.027v1.56l2.217-
1.15c.287-.164.575-.205.862-.205 2.546 0 3.983 2.217 3.983 4.352 0 3.45-2.463 5.79-
5.543 6.16zm.534-8.993c-.657 0-1.519.452-2.053.78v6.077c.452.493 1.191.862 2.094.862
1.191 0 2.751-.903 2.751-3.982 0-2.587-1.232-3.737-2.792-3.737zm12.81
1.027c-.246-.329-.575-.411-.985-.411-.534 0-1.191.616-1.643 1.889v3.819c0 1.396.164
1.52 1.93 1.643v.821h-5.584v-.821c1.396-.123 1.561-.247 1.561-1.643v-4.64c0-1.396-.123-
1.396-1.396-1.643v-.698c1.232-.247 2.423-.493 3.49-.903v2.464h.041c.739-1.355 1.766-
2.422 2.71-2.422.822 0 1.396.616 1.396 1.273 0 .943-.985 1.765-1.52 1.272zm7.844
7.761h-5.256v-.821c1.396-.123 1.601-.247 1.601-1.724v-4.435c0-1.601-.123-1.601-1.478-
1.766v-.698c1.273-.247 2.545-.534 3.572-.903v7.802c0 1.478.123 1.601 1.561 1.724zm-
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1.437 1.437 0 .78-.615 1.396-1.437 1.396zm15.275 12.524h-4.845v-.821c1.15-.123
1.314-.247 1.314-1.561v-4.024c0-1.478-.657-2.382-1.889-2.382-.78 0-1.684.575-2.3
1.15v5.256c0 1.314.124 1.438 1.273 1.561v.821h-5.01v-.821c1.396-.123 1.601-.247 1.601-
1.561v-4.722c0-1.396-.082-1.478-1.314-1.643v-.698c1.232-.247 2.382-.493
3.449-.903v1.643c.534-.452 2.094-1.601 3.285-1.601 1.848 0 2.997 1.273 2.997
3.162v4.763c0 1.314.206 1.438 1.438 1.561v.82zm11.702-9.773c-.164.369-.616 1.068-.985
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0-.452-.041-.739-.041-.493.164-.903.739-.903 1.108 0 .37.37.822 1.355.822H89.6c1.437 0
3.367.698 3.367 2.997 0 2.628-2.751 4.845-5.954 4.845-2.792 0-4.271-1.724-4.271-3.121
0-.903.452-1.601 2.382-3.08-.698-.246-1.93-.944-1.848-2.258.945-.41 1.807-1.15 2.176-
1.601-1.108-.37-2.135-1.684-2.135-3.161 0-2.669 2.382-4.106 4.352-4.106a5.1 5.1 0
012.382.575c1.068-.041 2.135-.164 3.121-.287zm-3.243 11.005c-.575-.206-1.355-.247-
2.628-.247-1.766 0-2.546 1.314-2.546 2.3 0 1.396 1.232 2.464 3.08 2.464 2.053 0 3.203-
1.355 3.203-2.71-.001-.863-.494-1.561-1.109-1.807zm-2.628-10.553c-.862 0-1.848.903-
1.848 2.628s.903 2.957 2.135 2.957c.903 0 1.766-.78 1.766-2.669 0-1.602-.781-2.916-
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3.859.903 0 1.56-.246 2.381-1.067l.534.739c-1.355 1.683-2.957 2.094-3.696 2.094-2.915
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3.655.001.615-.123.862-.574.944zm-3.49-3.572c-.944 0-1.93 1.027-2.176
2.792l3.531-.082c.452 0 .534-.123.534-.534-.001-1.109-.78-2.176-1.889-2.176zm11.825
1.519a1.402 1.402 0 00-.985-.411c-.534 0-1.232.616-1.683 1.889v3.819c0 1.396.164 1.52
1.929 1.643v.821h-5.625v-.821c1.437-.123 1.56-.247 1.56-1.643v-4.64c0-1.396-.082-1.396-
1.396-1.643v-.698c1.314-.247 2.464-.493 3.531-.903v2.464h.041c.698-1.355 1.724-2.422
2.71-2.422.78 0 1.396.616 1.396 1.273 0 .943-1.026 1.765-1.478 1.272z"/></symbol>
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2.875 2.956-2.875 4.434H3.696l.041-1.232-.986.821-2.628-3.038S0 14.233 0
14.11c0-.123.041-.206.041-.206l4.147-5.625.739-2.217 1.109-.41 1.15-1.601-.411-
2.794c1.108-.411 2.176-.041 2.71.492A14.315 14.315 0 009.444.025c1.971-.205 2.668.862
2.997 2.053a13.98 13.98 0 011.478.206.669.669 0 01.616-.452c.369 0
.616.287.616.616v.164c.863.287 1.684.698 2.423 1.15a.585.585 0 01.492-.247c.37 0
.616.287.616.616 0 .164-.041.287-.123.37.698.575 1.273 1.273 1.807 2.012a.76.76 0
01.287-.082c.369 0 .657.287.657.616 0 .247-.123.452-.328.534.411.739.739 1.56.985
2.422.041-.041.123-.041.164-.041.369 0 .616.287.616.616s-.205.575-.451.616c.164.862.287
1.725.369 2.628.369 0 .657.287.657.616 0 .369-.287.615-.616.657 0 .862-.041 1.807-.123
2.71a.664.664 0 01.575.657c0 .329-.287.616-.657.616h-.041c-.164.903-.328 1.806-.534
2.751h1.725v1.191zm-2.957-1.15c2.382-9.814-.411-17.615-8.007-18.519.041.411.041.739.041
1.068 0 .493-.041.903-.041.903l-1.19-.206c.041-.411.123-3.203-.863-3.818 0 0 0
1.478-.328 2.956L9.198 4.05c0-1.027-.452-1.437-1.067-1.725l.287 2.012-.699
1.027.329.944-2.176.739-.616 1.766-3.819 5.256 1.438 1.724 1.601-
1.355.369.246v2.012h.862c.37-1.437 1.56-3.121 2.669-3.942l-.616-.739.903-.78.862
1.068s3.08 0 3.08-.041c.452-.985.739-2.176.739-3.572h1.191c0 4.681-2.34 6.529-5.256
9.403-1.068 1.067-2.012 2.217-2.135 3.777h13.55zM3.573 12.796c.041.534-.041 1.355-.329

1.766l-.862-.329c.287-.41.452-.985.452-1.478l.739.041zm4.721-4.558l-1.847.985-.124-
1.519 1.93-.206.041.74z" fill-rule="nonzero"/><path d="M23.651 29.097H4.27v-
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2.505-.411-3.983l.945-.164c.534 2.012 1.273 3.983 3.736 3.983 1.725 0 2.751-1.068
2.751-2.669 0-4.229-7.021-3.284-7.021-8.171 0-2.217 1.807-4.229 5.01-4.229 1.068 0
2.217.287 3.367.698.082.862.164 1.848.205 3.573l-.862.041c-.411-1.438-1.067-3.203-
3.162-3.203-1.56 0-2.341 1.068-2.341 2.341 0 3.901 7.145 3.08 7.145 8.171 0 2.421-2.177
4.515-5.379 4.515zm11.702-.164c-.657-.041-1.191-.164-1.519-.287v3.859c0 1.396.164 1.52
2.053 1.684v.78h-5.789v-.78c1.478-.164 1.601-.287 1.601-1.684V15.793c0-1.437-.041-
1.478-1.437-1.601v-.698c1.232-.246 2.381-.616 3.572-1.027v1.56l2.217-
1.15c.287-.164.575-.205.862-.205 2.546 0 3.983 2.217 3.983 4.352 0 3.45-2.463 5.79-
5.543 6.16zm.534-8.993c-.657 0-1.519.452-2.053.78v6.077c.452.493 1.191.862 2.094.862
1.191 0 2.751-.903 2.751-3.982 0-2.587-1.232-3.737-2.792-3.737zm12.81
1.027c-.246-.329-.575-.411-.985-.411-.534 0-1.191.616-1.643 1.889v3.819c0 1.396.164
1.52 1.93 1.643v.821h-5.584v-.821c1.396-.123 1.561-.247 1.561-1.643v-4.64c0-1.396-.123-
1.396-1.396-1.643v-.698c1.232-.247 2.423-.493 3.49-.903v2.464h.041c.739-1.355 1.766-
2.422 2.71-2.422.822 0 1.396.616 1.396 1.273 0 .943-.985 1.765-1.52 1.272zm7.844
7.761h-5.256v-.821c1.396-.123 1.601-.247 1.601-1.724v-4.435c0-1.601-.123-1.601-1.478-
1.766v-.698c1.273-.247 2.545-.534 3.572-.903v7.802c0 1.478.123 1.601 1.561
1.724v.821zm-2.711-12.524c-.78 0-1.396-.616-1.396-1.396 0-.821.616-1.437 1.396-
1.437.822 0 1.437.616 1.437 1.437 0 .78-.615 1.396-1.437 1.396zm15.275 12.524h-
4.845v-.821c1.15-.123 1.314-.247 1.314-1.561v-4.024c0-1.478-.657-2.382-1.889-2.382-.78
0-1.684.575-2.3 1.15v5.256c0 1.314.124 1.438 1.273 1.561v.821h-5.01v-.821c1.396-.123
1.601-.247 1.601-1.561v-4.722c0-1.396-.082-1.478-1.314-1.643v-.698c1.232-.247
2.382-.493 3.449-.903v1.643c.534-.452 2.094-1.601 3.285-1.601 1.848 0 2.997 1.273 2.997
3.162v4.763c0 1.314.206 1.438 1.438 1.561v.82h.001zm11.702-9.773c-.164.369-.616
1.068-.985 1.273l-1.191-.123c.329.452.575 1.355.575 2.053 0 2.505-2.258 3.86-4.311
3.86-.123 0-.452-.041-.739-.041-.493.164-.903.739-.903 1.108 0 .37.37.822
1.355.822H89.6c1.437 0 3.367.698 3.367 2.997 0 2.628-2.751 4.845-5.954 4.845-2.792 0-
4.271-1.724-4.271-3.121 0-.903.452-1.601 2.382-3.08-.698-.246-1.93-.944-1.848-
2.258.945-.41 1.807-1.15 2.176-1.601-1.108-.37-2.135-1.684-2.135-3.161 0-2.669 2.382-
4.106 4.352-4.106a5.1 5.1 0 012.382.575c1.068-.041 2.135-.164 3.121-.287l.163.245zm-
3.243 11.005c-.575-.206-1.355-.247-2.628-.247-1.766 0-2.546 1.314-2.546 2.3 0 1.396
1.232 2.464 3.08 2.464 2.053 0 3.203-1.355 3.203-2.71-.001-.863-.494-1.561-1.109-
1.807zm-2.628-10.553c-.862 0-1.848.903-1.848 2.628s.903 2.957 2.135 2.957c.903 0
1.766-.78 1.766-2.669 0-1.602-.781-2.916-2.053-2.916zm14.494 3.613c-.369.041-3.203.246-
5.789.329.082 2.71 1.683 3.859 3.285 3.859.903 0 1.56-.246 2.381-1.067l.534.739c-1.355
1.683-2.957 2.094-3.696 2.094-2.915 0-4.599-2.217-4.599-4.845 0-3.203 2.423-5.708
4.845-5.708 2.012 0 3.613 1.725 3.613 3.655.001.615-.123.862-.574.944zm-3.49-
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1.109-.78-2.176-1.889-2.176zm11.825 1.519a1.402 1.402 0 00-.985-.411c-.534 0-1.232.616-
1.683 1.889v3.819c0 1.396.164 1.52 1.929 1.643v.821h-5.625v-.821c1.437-.123 1.56-.247
1.56-1.643v-4.64c0-1.396-.082-1.396-1.396-1.643v-.698c1.314-.247 2.464-.493
3.531-.903v2.464h.041c.698-1.355 1.724-2.422 2.71-2.422.78 0 1.396.616 1.396 1.273 0
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3.039s-.123-.165-.123-.287c0-.123.041-.205.041-.205l4.154-5.626.739-2.217 1.111-.411
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1.974-.205 2.672.863 3.001 2.053.534.041 1.028.123 1.482.206a.67.67 0 01.617-.453c.37 0
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.617.287.617.615 0 .166-.041.288-.123.37.698.575 1.275 1.273 1.81 2.012a.762.762 0
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1.725.371 2.627.371 0 .657.288.657.616 0 .37-.288.615-.616.657 0 .861-.041 1.807-.124
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00-1.57-.93A5.37 5.37 0 0185 8a2.5 2.5 0 01-.7-1.74 2.23 2.23 0 01.85-1.82 3.2 3.2 0 012.08-.69 3.56 3.56 0 012.39.82l.06 1.41h-.2a3 3 0 00-2.32-1.18 1.87 1.87 0 00-1.23.4 1.26 1.26 0 00-.48 1c0 .87.77 1.49 2.2 2.11 1.75.74 2.71 1.7 2.71 3a2.89 2.89 0 01-.94 2.21 3.27 3.27 0 01-2.35.88 4.06 4.06 0 01-2.94-1.18l.08-1.53zm8.31-3.88a3.62 3.62 0 012.55-1.09 3.43 3.43 0 012.53 1 3.48 3.48 0 011 2.58v.59h-6a2.71 2.71 0 00.47 1.35 2.53 2.53 0 002.13 1.12 3.5 3.5 0 001.38-.26 5 5 0 001.37-.94h.11v1.29a4.4 4.4 0 01-2.78 1 3.84 3.84 0 01-1.95-.51A3.7 3.7 0 0192 12.52a3.91 3.91 0 01-.49-1.95 3.9 3.9 0 011.07-2.75zm5 2.08a2.44 2.44 0 00-.78-1.6 2.33 2.33 0 00-1.67-.62 2.26 2.26 0 00-1.52.58 2.62 2.62 0 00-.86 1.62h4.83zm2.56 4.3V6.93h1.18V8a2.51 2.51 0 01.92-.94 2.31 2.31 0 011.16-.32 1.86 1.86 0 011.11.34l.08 1.19h-.14a1.71 1.71 0 00-1.24-.48 1.87 1.87 0 00-1.28.51 2.35 2.35 0 00-.62 1.75v4.15h-1.18zM106 4.14a.82.82 0 110 1.16.83.83 0 010-1.16zm0 10.06V6.93h1.18v7.27H106zm3.75-6.38a3.62 3.62 0 012.55-1.09 3.43 3.43 0 012.53 1 3.48 3.48 0 011 2.58v.59h-6a2.7 2.7 0 00.47 1.35 2.53 2.53 0 002.13 1.12 3.51 3.51 0 001.39-.26 5 5 0 001.34-.92h.11v1.29a4.36 4.36 0 01-2.78 1 3.83 3.83 0 01-1.94-.51 3.67 3.67 0 01-1.36-1.39 4.08 4.08 0 01.58-4.7zm5 2.08a2.46 2.46 0 00-.77-1.6 2.31 2.31 0 00-1.66-.62 2.26 2.26 0 00-1.52.58 2.62 2.62 0 00-.86 1.62h4.83zm2.42 2.65h.09a3.38 3.38 0 002.08.79c.92 0 1.48-.43 1.48-1.08a1 1 0 00-.4-.81 5 5 0 00-1.29-.59 4.14 4.14 0 01-1.4-.74 1.84 1.84 0 01-.62-1.43 1.73 1.73 0 01.69-1.37 2.51 2.51 0 011.68-.58 3.87 3.87 0 012 .56l.05 1.13h-.1a3.16 3.16 0 00-2-.7c-.75 0-1.31.35-1.31 1a.89.89 0 00.42.77 5.83 5.83 0 001.31.61 4.46 4.46 0 011.55.81 1.69 1.69 0 01.57 1.35 2 2 0 01-.78 1.59 2.92 2.92 0 01-1.88.63 4.35 4.35 0 01-2.43-.74l.28-1.12zM34.72 8.54a4.21 4.21 0 002.63-3.9 4.07 4.07 0 00-1.58-3.36A7.06 7.06 0 0031.28 0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8 4.1 4.1 0 00-1-2.8 5 5 0 00-2.5-1.56zm-6.07 1.84h3.25c1.74 0 2.6.72 2.6 2.21s-.84 2.21-2.6 2.21h-3.25zm4.64-3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0 01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79 17.94h3.59l2.6-9.36 4 8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0 014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-2.7-.32 9.78 9.78 0 00-4.66 1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.7 3.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0 002.37-1l-.83-3.18zM0 .01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97 17.97z"/></symbol><symbol id="icon-logo-bmc-white-aj" viewBox="0 0 76 18"><path d="M34.72 8.53a4.21 4.21 0 002.63-3.9 4.07 4.07 0 00-1.58-3.36A7.06 7.06 0 0031.28 0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8 4.1 4.1 0 00-1-2.8 5 5 0 00-2.5-1.57zm-6.07 1.84h3.25c1.74 0 2.6.72 2.6 2.21s-.84 2.21-2.6 2.21h-3.25zm4.64-3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0 01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79 17.94h3.59l2.6-9.36 4 8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0 014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-2.7-.32 9.78 9.78 0 00-4.66 1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.7 3.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0 002.37-1l-.83-3.18zM0 .01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97 17.97z"/></symbol><symbol id="icon-logo-bmc-white-flagship" viewBox="0 0 76 18"><path d="M34.72 8.53a4.21 4.21 0 002.63-3.9 4.07 4.07 0 00-1.58-3.36A7.06 7.06 0 0031.28 0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8 4.1 4.1 0 00-1-2.8 5 5 0 00-2.5-1.57zm-6.07 1.84h3.25c1.74 0 2.6.72 2.6 2.21s-.84 2.21-2.6 2.21h-3.25zm4.64-3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0 01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79 17.94h3.59l2.6-9.36 4 8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0 014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-2.7-.32 9.78 9.78 0 00-4.66 1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.7 3.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0 002.37-1l-.83-3.18zM0 .01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97 17.97z"/></symbol><symbol id="icon-logo-bmc-white-series" viewBox="0 0 76 18"><path d="M34.72 8.53a4.21 4.21 0 002.63-3.9 4.07 4.07 0 00-1.58-3.36A7.06 7.06 0 0031.28 0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8

4.1 4.1 0 00-1-2.8 5 5 0 00-2.5-1.57zm-6.07 1.84h3.25c1.74 0 2.6.72 2.6 2.21s-.84 2.21-2.6 2.21h-3.25zm4.64-3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0 01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79 17.94h3.59l2.6-9.36 4 8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0 014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-2.7-.32 9.78 9.78 0 00-4.66 1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.73.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0 002.37-1l-.83-3.18zM0 .01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97 17.97z"/></symbol><symbol id="icon-logo-bmc-white-series_flagship" viewBox="0 0 76 18"><path d="M34.72 8.53a4.21 4.21 0 002.63-3.9 4.07 4.07 0 00-1.58-3.36A7.06 7.06 0 0031.28 0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8 4.1 4.1 0 00-1-2.8 5 5 0 00-2.5-1.57zm-6.07 1.84h3.25c1.74 0 2.6.72 2.6 2.21s-.84 2.21-2.6 2.21h-3.25zm4.64-3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0 01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79 17.94h3.59l2.6-9.36 4 8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0 014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-2.7-.32 9.78 9.78 0 00-4.66 1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.73.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0 002.37-1l-.83-3.18zM0 .01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97 17.97z"/></symbol><symbol id="icon-logo-bmc-white-strapline-sn" viewBox="0 0 173 16"><path d="M0 12V.23h3a4.34 4.34 0 013 1.08 3.41 3.41 0 011 2.48 3.42 3.42 0 01-1 2.48 4.38 4.38 0 01-3 1.07H1.51V12zm1.51-5.9H3a2.84 2.84 0 001.87-.58 2.05 2.05 0 00.71-1.69 2.05 2.05 0 00-.71-1.73A2.8 2.8 0 003 1.51H1.51zm12.92-1.38v-1h1.33V12h-1.33v-1a3.87 3.87 0 01-2.91.28A4.26 4.26 0 017.76 10a4.52 4.52 0 01-.56-2.2 4.47 4.47 0 01.56-2.19A4.14 4.14 0 019.31 4a4.25 4.25 0 012.21-.59 3.86 3.86 0 012.91 1.31zM8.55 7.83a3.25 3.25 0 00.82 2.25 2.75 2.75 0 002.16.92 2.75 2.75 0 002.16-.92 3.25 3.25 0 00.83-2.25 3.25 3.25 0 00-.83-2.25 2.75 2.75 0 00-2.16-.92 2.75 2.75 0 00-2.16.92 3.25 3.25 0 00-.82 2.25zm8.64.17V3.68h1.34V4.9a2.87 2.87 0 011-1.07 2.63 2.63 0 011.32-.37 2.12 2.12 0 011.27.38l.09 1.36h-.16a2 2 0 00-1.41-.54 2.11 2.11 0 00-1.46.58 2.67 2.67 0 00-.72V12zm6.06-7.1V3.68h1.59V1.94l1.34-.64v2.38h2.36V4.9h-2.36V10a.94.94 0 00.32.77 1.18 1.18 0 00.75.25 2.12 2.12 0 001.24-.48h.15l-.1 1.27a4 4 0 01-.78.33 2.68 2.68 0 01-.78.1 2.1 2.1 0 01-1.57-.6 2.32 2.32 0 01-.58-1.67v-5zm11.87 2.93a4.34 4.34 0 01.68 0 4.34 4.34 0 011-8.68 0zm6.49 2.28a3.17 3.17 0 00.85-2.28 3.17 3.17 0 00-.85-2.28 3 3 0 00-4.3 0 3.17 3.17 0 00-.85 2.28 3.17 3.17 0 00.85 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2.94v.67h-6.78a3.1 3.1 0 00.53 1.54 2.88 2.88 0 002.43 1.28 4 4 0 001.58-.29 5.77 5.77 0 001.52-1h.13v1.47a5 5 0 01-3.17 1.09 4.32 4.32 0 01-2.21-.58 4.17 4.17 0 01-1.59-1.69 4.54 4.54 0 01-.56-2.22 4.52 4.52 0 011.22-3.08zm5.69 2.37a2.79 2.79 0 00-.88-1.82 2.69 2.69 0 00-1.9-.7 2.6 2.6 0 00-1.73.66 3 3 0 00-1 1.85zM112 12V3.68h1.34V4.9a2.87 2.87 0 011-1.07 2.63 2.63 0 011.32-.37 2.12 2.12 0 011.27.38L117 5.2h-.16a2 2 0 00-1.41-.54 2.12 2.12 0 00-1.46.58 2.67 2.67 0 00-.7 2V12zm11.93 0V.23h.57l6.89 8.25V.23h1.51V12h-.57l-6.88-8.29V12zm17.41-7.28v-1h1.33V12h-1.33v-1a3.87 3.87 0 01-2.91.28 4.26 4.26 0 01-3.76-2.28 4.52 4.52 0 01-.56-2.2 4.46 4.46 0 01.56-2.19A4.14 4.14 0 01136.23 4a4.25 4.25 0 012.21-.59 3.86 3.86 0 012.9 1.31zm-5.88 3.1a3.25 3.25 0 00.82

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3.25 0 00-.82 2.26zM144 4.9V3.68h1.59V1.94l1.34-.64v2.38h2.36V4.9h-2.36V10a.94.94 0
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1.93 0 00.54 1.45A2 2 0 00154 11a2.24 2.24 0 001.73-.77 2.75 2.75 0 00.71-
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2.12 0 011.27.38l.09 1.36h-.16a2 2 0 00-1.41-.54 2.11 2.11 0 00-1.46.58 2.67 2.67 0
00-.7 2V12zm6.71-7.3a4.13 4.13 0 012.9-1.24 3.9 3.9 0 012.88 1.11A4 4 0 01173
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4.54 4.54 0 01-.56-2.22 4.52 4.52 0 011.23-3.08zm5.69 2.37a2.79 2.79 0 00-.88-1.82 2.69
2.69 0 00-1.9-.7 2.6 2.6 0 00-1.73.66 3 3 0 00-1 1.85z"/></symbol><symbol id="icon-
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2.3 4.8 4.8 0 00.83-2.8 4.1 4.1 0 00-1-2.8 5 5 0 00-2.48-1.57zm-6.07 1.84H7c1.74 0
2.6.72 2.6 2.21s-.88 2.21-2.6 2.21H3.71zm4.64-3.72a2.81 2.81 0 01-2 .55H3.71v-
4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0 01-.52 1.47zM31.12 0h-1.17l-4.66
10.61L20.67 0H19.5l-4.79 17.94h3.59l2.59-9.36 4 8.65h.81l4-8.65L32.24 18h3.59zm19.1
13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0140.35 9a5.78 5.78 0
011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0 014 1.27L51 1.39A9.76 9.76 0 0048.67.32
10.22 10.22 0 0046 0a9.78 9.78 0 00-4.65 1.14A8.48 8.48 0 0038 4.36 9 9 0 0036.78
9a9.13 9.13 0 00.7 3.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0046 18a10.06 10.06 0
002.7-.31 9.79 9.79 0 002.37-1l-.82-3.18z"/></symbol><symbol id="icon-logo-bmc-white"
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3.36A7.06 7.06 0 0031.28 0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8 4.1
4.1 0 00-1-2.8 5 5 0 00-2.5-1.57zm-6.07 1.84h3.25c1.74 0 2.6.72 2.6 2.21s-.84 2.21-2.6
2.21h-3.25zm4.64-3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0
01.52 1.46 2 2 0 01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79
17.94h3.59l2.6-9.36 4 8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3
5.66 5.66 0 01-4.25-1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0
014.25-1.61 7.19 7.19 0 014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-
2.7-.32 9.78 9.78 0 00-4.66 1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.7
3.59 8.55 8.55 0 001.93 2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0
002.37-1l-.83-3.18zM0 .01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97
17.97z"/></symbol><symbol id="icon-logo-bmc" viewBox="0 0 76 18"><path d="M34.72
8.53a4.21 4.21 0 002.63-3.9 4.07 4.07 0 00-1.58-3.36A7.06 7.06 0 0031.28
0H25v18h7.26a5.93 5.93 0 005.13-2.3 4.8 4.8 0 00.83-2.8 4.1 4.1 0 00-1-2.8 5 5 0 00-
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3.72a2.81 2.81 0 01-2 .55h-2.64v-4h2.64a2.81 2.81 0 012 .52 2 2 0 01.52 1.46 2 2 0
01-.52 1.47zM56.05 0h-1.16l-4.66 10.61L45.65 0h-1.21l-4.79 17.94h3.59l2.6-9.36 4
8.65h.81l4-8.65L57.18 18h3.59zm19.11 13.49a7.19 7.19 0 01-4 1.3 5.66 5.66 0 01-4.25-
1.61A5.84 5.84 0 0165.29 9a5.78 5.78 0 011.54-4.15 5.66 5.66 0 014.25-1.61 7.19 7.19 0
014 1.27l.81-3.12A9.76 9.76 0 0073.61.32a10.22 10.22 0 00-2.7-.32 9.78 9.78 0 00-4.66
1.14A8.48 8.48 0 0063 4.36 9 9 0 0061.76 9a9.13 9.13 0 00.7 3.59 8.55 8.55 0 001.93
2.86A9.51 9.51 0 0070.93 18a10.06 10.06 0 002.7-.31 9.79 9.79 0 002.37-1l-.83-3.18zM0
.01h17.97v17.97L0 .01z"/><path d="M17.97 17.98H0V.01l17.97 17.97z"/></symbol><symbol
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0 4.69 1.32 4.69 4.11a3.34 3.34 0 01-2.42 3.34c2.4.46 3.1 2 3.1 4.09 0 2.86-1.52 4.49-
4.82 4.49H1.77c-.48 0-.57-.09-.57-.62V.9c0-.39.08-.48.55-.48zm8.12 4.11c0-2-.88-2.84-
3.5-2.84H2.54v5.73h4c2.05 0 3.32-.95 3.32-2.89zm.68 7.47c0-2.35-.84-3.28-3.37-
3.28H2.54v6.53h4.27c2.19-.02 3.74-.73 3.74-3.25zm4.7 4V.86c0-.37 0-.44.44-.44h.51c.33 0
.42.07.59.42l4.82 9.83a5.72 5.72 0 01.31.7 5.6 5.6 0
01.33-.79L27.11.79c.18-.33.24-.37.57-.37h.51c.37 0 .44.07.44.42v15.22c0
.37-.07.44-.46.44h-.42c-.4 0-.46-.09-.46-.44V5a12.69 12.69 0 01.11-2h-.07a16.64 16.64 0
01-.81 1.87l-3.83 7.75c-.15.24-.22.42-.51.42h-.42c-.33 0-.42-.09-.57-.4l-3.89-
8c-.29-.59-.59-1.32-.77-1.78a19.37 19.37 0 01.09 2v11.2c0 .37-.07.44-.46.44h-.42c-.42
0-.49-.06-.49-.5zm16.81-6.34V7.22c0-4.4 1.61-7.11 6-7.11a9.23 9.23 0 014
.77c.44.22.57.33.57.55a1 1 0 01-.09.4c-.13.29-.26.42-.44.42a4.83 4.83 0 01-.92-.33 8.18
8.18 0 00-3-.53c-4 0-4.8 2.53-4.8 6v2.27c0 4.55 1.83 5.87 4.75 5.87a7.74 7.74 0 003.67-
1 1.89 1.89 0 01.66-.26c.15 0 .24.09.37.33a1 1 0 01.15.46c0 .31-.29.42-.81.7a8.74 8.74
0 01-4.11 1c-3.95.05-6-2.13-6-7.1zM53.27 2V.75c0-.4.07-.46.48-.46h.51c.44 0
.48.07.48.46V2c0 .4-.07.46-.51.46h-.46c-.41-.04-.5-.11-.5-.46zm.09
14V4.77c0-.35.07-.44.44-.44h.42c.4 0 .46.07.46.42V16c0
.37-.09.46-.46.46h-.42c-.36.04-.44-.02-.44-.46zm4.48-.51a.78.78 0
01.09-.37c.07-.15.2-.42.4-.42a1.64 1.64 0 01.53.18 9.07 9.07 0 003.39.59c2 0 3.08-.95
3.08-2.51 0-1.39-.59-2.09-3.5-2.35-2.68-.24-4-1.19-4-3.21a2.86 2.86 0 011.36-2.6 5.65
5.65 0 013-.73 10.53 10.53 0 013 .4c.37.11.7.24.7.46a1.15 1.15 0
01-.13.46c-.09.18-.18.42-.37.42a5.49 5.49 0 01-.66-.2 9.09 9.09 0 00-2.49-.35 4 4 0 00-

2.4.57 1.75 1.75 0 00-.75 1.52c0 1.39.81 1.83 3.08 2.07 3.21.31 4.4 1.43 4.4 3.45 0
2.38-1.52 3.78-4.42 3.78a10.91 10.91 0 01-3.3-.48c-.54-.17-1.01-.42-
1.01-.68zm20.49-.75v5.52c0 .4-.07.46-.48.46h-.37c-.37 0-.46-.07-.46-.48v-
14c0-.73.07-.88.51-1.08a8.35 8.35 0 014.25-1.1h.13c3.43 0 4.77 2.07 4.77 5.54v1.5c0
3.39-1.45 5.61-4.53 5.61H82a4.07 4.07 0 01-3.67-1.97zm.24-
8.69c-.29.15-.29.2-.29.55v5.61a3.42 3.42 0 003.54 3.3h.11c2.27 0 3.34-1.54 3.34-
4.55V9.68c0-2.84-.9-4.4-3.48-4.4h-.13a6.13 6.13 0 00-3.09.77zm14.89-.79a6.89 6.89 0 00-
2.77.53 2.08 2.08 0 01-.62.15c-.2 0-.29-.11-.4-.37a1.17 1.17 0
01-.11-.42c0-.22.26-.33.84-.55a8.83 8.83 0 013-.53c3.5 0 4.31 1.8 4.31 4.09v5.1a4.25
4.25 0 00.59 2.35 1 1 0 01.22.46c0 .15-.09.24-.29.37l-.2.11a.68.68 0 01-.37.15c-.13
0-.22 0-.42-.33a4.9 4.9 0 01-.66-1.85 4.25 4.25 0 01-3.94 2.2c-2.18 0-3.65-1.1-3.65-
3.59 0-2.79 1.91-4 6.54-4h.92v-1c0-1.86-.7-2.87-3-2.87zm-.62 10.3c2.2 0 3.61-1.39 3.61-
4.09v-1.22h-.95c-4 0-5.19.95-5.19 2.88s1 2.43 2.54 2.43zm9.38-11.23h.2c.33 0
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01-.11.48c-.09.29-.18.42-.4.42a7.32 7.32 0 00-2-.46c-1.69 0-2.64 1.23-2.64 3.28V16c0
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3.12l.4-.18a.83.83 0 01.37-.11c.26 0 .29.13.29.48v3.18h3.3c.42 0 .51.07.51.46v.29c0
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.22.07.33.33a1.33 1.33 0 01.18.53c0 .15-.13.22-.29.29a5.86 5.86 0 01-2.31.46c-1.69 0-
2.88-.9-2.88-3.28V5.79h-1c-.37 0-.44-.11-.44-.37v-.1c0-.29.15-.33.75-.46a.81.81 0
00.68-.88V1.69c0-.26 0-.37.24-.48zM130 4.07h.35c3.34 0 4.75 1.87 4.75 5.59v1.41c0 3.81-
1.45 5.68-4.82 5.68h-.37c-3.26 0-4.73-1.83-4.73-5.65V9.7c0-3.85 1.54-5.63 4.82-
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3.54-1.74 3.54-4.58V9.81c.05-2.88-.74-4.53-3.47-4.53zM141.53 0a5.55 5.55 0 012
.37c.37.15.57.24.57.48a1.22 1.22 0 01-.07.4c-.09.26-.18.42-.35.42a1.82 1.82 0
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0-.46-.07-.46-.48V5.77h-1c-.37
0-.46-.11-.46-.37v-.1c0-.26.18-.33.77-.44s.68-.37.68-.7V3.3c0-2.3 1.15-3.3 3-3.3zM7.38
32.42c-1.43-.64-2.67-1.19-2.67-2.25a1.74 1.74 0 011.92-1.75 9.27 9.27 0 013.6 1l1.48-
2.81a10.89 10.89 0 00-5.4-1.42c-3.7 0-5.92 1.89-5.92 5S3 34.57 5.07 35.55c1.51.71 2.81
1.33 2.81 2.48 0 1-.94 1.67-2.33 1.67a9.66 9.66 0 01-4.06-1.16L0 41.55a11.87 11.87 0
005.89 1.55c3.85 0 6.15-2 6.15-5.41-.04-3.2-2.59-4.35-4.66-5.27zm12.41-5.25h-
5.43v15.59h4.09V38h1.24c1.86 0 6.19-.57 6.19-5.84-.01-3.21-2.17-4.99-6.09-4.99zm-.13
7.93h-1.22v-5h1.26c1.89 0 2.27 1 2.27 2.7s-.7 2.3-2.31 2.3zm18.07 1.64a5.45 5.45 0
002.11-4.48c0-3.74-3.37-5.07-6.53-5.07h-5.43v15.57H32V38h1.94a11.52 11.52 0 011.82
4.75h4.54a16.91 16.91 0 00-2.54-6zm-4.5-1.64H32v-5h1.26c1.89 0 2.27 1 2.27 2.7s-.72
2.32-2.32 2.32zm9.65 7.66H47V27.19h-4.12zm17-5.38L55 27.19h-4.44v15.57h3.6v-9.82l5.08
9.82h4.31V27.19h-3.63v10.19zm13.46-.48h1.7v3.18a8 8 0 01-1.8.21c-2.16 0-3-1.51-3-5.39
0-3.41 1.24-5.06 3.8-5.06a8.88 8.88 0 013.43 1l1.11-2.6a10.53 10.53 0 00-5.17-1.41c-
2.48 0-4.26.66-5.46 2s-1.78 3.38-1.78 6.17c0 6 1.85 8.28 6.84 8.28A14.44 14.44 0
0078.76 42v-7.75h-5.39zm12.08-.6h5.3v-3h-5.3v-3.07h5.79v-3h-9.66V40a3.07 3.07 0 00.83
2.07 3.13 3.13 0 002.26.79c3 0 6.23-.09 6.69-.1v-3h-5.87v-3.45zm18.7.48a5.45 5.45 0
002.11-4.48c0-3.74-3.37-5.07-6.53-5.07h-5.43v15.53h4.09V38h1.94a11.52 11.52 0 011.82
4.75h4.47a17 17 0 00-2.43-5.96zm-4.49-1.68h-1.21v-5h1.26c1.89 0 2.27 1 2.27 2.7s-.71
2.3-2.32 2.3zM123 37.49l-6-12.18h-4.77v17.45H116v-12l6 12h4.83V25.31H123v12.18zm20.58-
7.12h3.68v12.4h4.26v-12.4h3.14v-3.18h-11.05v3.18zm21.85 7.2c0 1.59-.1 2.57-2 2.57s-
2.11-.8-2.11-2.59V27.19h-4.23v10.56c0 3.71 1.9 5.37 6.16 5.37s6.39-1.88 6.39-5.93v-10h-
4.23v10.37zm25.92 2.16v-3.42h5.3v-3h-5.3v-3.08h5.79v-3h-9.69V40a3.07 3.07 0 00.83 2.07
3.13 3.13 0 002.26.79c3 0 6.23-.09 6.69-.1v-3h-5.86zm-58.21-12.54l-4 15.57h4.17l.59-
2.47h4.57l.59 2.47h4.4l-3.94-15.57zm1.24 10.16l1.7-6.77h.17l1.75 6.77zm48.13-.6a5.45
5.45 0 002.11-4.48c0-3.74-3.37-5.07-6.53-5.07h-5.43v15.56h4.09V38h1.95a11.53 11.53 0
011.82 4.75h4.47a16.9 16.9 0 00-2.54-6zM178 35.1h-1.22v-5h1.26c1.89 0 2.27 1 2.27
2.7s-.72 2.32-2.32 2.32z"/></symbol><symbol id="icon-error" viewBox="2.002 0 14 14">
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4.053 0l4.949 4.95L13.951 0l2.051 2.049L11.053 7l4.949 4.949z"/></symbol><symbol
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0-.277-.147-.277-.279 0-.383.933-1.282 1.203-1.557.846-.811 1.949-1.434 3.174-1.434.908
0 1.879.555 1.125 2.63l-1.526 4.167c-.126.32-.358.854-.358 1.198 0
.148.088.298.255.298.632 0 1.796-1.818 2.091-1.818.105 0 .252.134.252.321C11.717 11.345
9.245 14 7.11 14c-.763 0-1.289-.361-1.289-1.176 0-1.027.717-2.778.865-3.145l1.479-
3.756zm1.144-4.211C9.309.771 10.111 0 11.045 0c.845 0 1.457.577 1.457 1.456 0 .983-.804
1.709-1.757 1.709-.866-.001-1.436-.578-1.436-1.453z"/></symbol><symbol id="icon-
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8.641L1.717 5.595 0 6.979l6.717 6.832c1.157-2.961 4.817-8.748 9.287-12.86L15.592 0z"/>
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11.211h2.789V14H7.002v-2.789zM7.002 0v3.436l.741 5.326h1.326l.723-5.326V0h-2.79z"/>
</symbol><symbol id="icon-facebook-bordered" viewBox="463.812 263.868 32 32"><path

d="M479.812 263.868c-8.837 0-16 7.163-16 16s7.163 16 16 16 16-7.163 16-16-7.163-16-16-16zm0 30c-7.732 0-14-6.269-14-14s6.268-14 14-14 14 6.269 14 14-6.267 14-14 14z"/><path d="M483.025 280.48l1.32-2.477h-2.453v-1.582c0-.715.199-1.207 1.227-1.207h1.311v-2.213a17.753 17.753 0 00-1.907-.098c-1.894 0-3.186 1.154-3.186 3.271V278h-2.142v2.477h2.142v6.354h2.557v-6.354l2.131.003z"/></symbol><symbol id="icon-twitter-bordered" viewBox="463.812 263.868 32 32"><path d="M486.416 276.191a5.622 5.622 0 01-1.554.429 2.718 2.718 0 001.19-1.502 5.456 5.456 0 01-1.72.657 2.71 2.71 0 00-1.979-.854 2.711 2.711 0 00-2.642 3.326 7.681 7.681 0 01-5.586-2.831 2.714 2.714 0 00.839 3.618 2.748 2.748 0 01-1.227-.339v.031a2.71 2.71 0 002.174 2.656 2.735 2.735 0 01-1.229.049 2.726 2.726 0 002.531 1.883 5.442 5.442 0 01-4.01 1.123 7.672 7.672 0 004.155 1.215c4.983 0 7.71-4.129 7.71-7.711 0-.115-.004-.232-.006-.351a5.41 5.41 0 001.354-1.399z"/><path d="M479.812 263.868c-8.837 0-16 7.163-16 16s7.163 16 16 16 16-7.163 16-16-7.163-16-16-16zm0 30c-7.732 0-14-6.269-14-14s6.268-14 14-14 14 6.269 14 14-6.267 14-14 14z"/></symbol><symbol id="icon-weibo-bordered" viewBox="463.812 263.868 32 32"><path d="M479.812 263.868c-8.838 0-16 7.163-16 16s7.162 16 16 16c8.837 0 16-7.163 16-16s-7.163-16-16-16zm0 30c-7.732 0-14-6.269-14-14s6.268-14 14-14c7.731 0 14 6.269 14 14s-6.267 14-14 14z"/><path d="M478.552 285.348c-2.616.261-4.876-.926-5.044-2.649-.167-1.722 1.814-3.33 4.433-3.588 2.609-.263 4.871.926 5.041 2.647.165 1.721-1.818 3.331-4.43 3.59m5.23-5.718c-.226-.065-.374-.109-.259-.403.25-.639.276-1.188.005-1.581-.515-.734-1.915-.693-3.521-.021 0 0-.508.224-.378-.181.247-.798.209-1.468-.178-1.852-.87-.878-3.194.032-5.183 2.027-1.489 1.494-2.357 3.082-2.357 4.453 0 2.619 3.354 4.213 6.631 4.213 4.297 0 7.154-2.504 7.154-4.493.001-1.198-1.007-1.881-1.914-2.162m2.855-4.797a4.176 4.176 0 00-3.982-1.291.608.608 0 00-.465.72.604.604 0 00.72.466 2.968 2.968 0 012.827.92 3 3 0 01.625 2.918.602.602 0 00.39.762.603.603 0 00.763-.391v-.001a4.218 4.218 0 00-.878-4.103"/><path d="M485.041 276.276a2.037 2.037 0 00-1.938-.63.518.518 0 00-.396.621.517.517 0 00.617.398c.336-.071.702.03.947.307s.312.649.207.979a.52.52 0 00.336.654.523.523 0 00.657-.336 2.038 2.038 0 00-.43-1.993m-6.347 5.951c-.09.156-.293.233-.451.166-.151-.062-.204-.235-.115-.389.093-.155.284-.229.44-.168.157.056.214.235.126.391m-.832 1.074c-.253.405-.795.58-1.202.396-.403-.186-.521-.655-.27-1.051.248-.39.771-.566 1.176-.393.413.17.543.636.296 1.048m.95-2.864c-1.244-.326-2.65.294-3.19 1.396-.553 1.119-.021 2.369 1.236 2.775 1.303.42 2.84-.225 3.374-1.436.526-1.183-.132-2.402-1.42-2.735"/></symbol><symbol id="icon-springer-hh" viewBox="0 0 164 30"><path d="M2.391 23v-9.3h2.392v-.87H2.391v-.567c0-1.818.287-3.449 1.976-3.449A2.747 2.747 0 015.514 9l1.286-.769a2.312 2.312 0 00-1.344-.287 2.876 2.876 0 00-2.1.86 4.8 4.8 0 00-.988 3.449v.573H0v.86h1.433v9.3h.988zm7.283-10.352c-2.3 0-4.308 1.818-4.308 5.376 0 3.36 1.818 5.178 4.121 5.178 2.1 0 4.308-1.532 4.308-5.277.039-3.35-1.729-5.277-4.121-5.277zm-.1.86c2.391 0 3.251 2.589 3.251 4.407.02 2.312-1.245 4.565-3.251 4.565s-3.251-2.2-3.251-4.506c-.009-2.065.95-4.466 3.252-4.466zM16.186 23h.988v-6.616c.247-1.532 1.117-2.8 2.589-2.8a.721.721 0 01.385.1V12.7a.721.721 0 00-.385-.1 2.965 2.965 0 00-2.678 2.115l-.1-1.917h-.9l.1 2.876V23zm9.882-14.19V23h.988v-7.1h6.917V23h.988V8.814h-.988v6.236h-6.917V8.814h-.988zm18.864 8.894v-.549c0-1.532-.573-4.506-3.538-4.506-2.391 0-4.121 2.115-4.121 5.465 0 2.965 1.63 5.079 4.308 5.079a6.3 6.3 0 002.777-.573l-.188-.771a4.723 4.723 0 01-2.391.484c-1.818 0-3.538-1.057-3.538-4.6h6.7zm-6.611-.771c.188-1.532 1.057-3.449 2.965-3.449s2.678 1.729 2.589 3.449h-5.554zm14.645-.484c0-1.976-.771-3.834-3.162-3.834a4.684 4.684 0 00-2.678.86l.306.7a3.725 3.725 0 012.2-.672c2.2 0 2.391 1.729 2.391 2.965v.287c-3.607.01-5.583 1.354-5.583 3.656a2.658 2.658 0 002.534 2.777q.121.006.243 0A3.261 3.261 0 0052 21.661h.1L52.2 23h.86a19.3 19.3 0 01-.1-2.4v-4.117zm-.988 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5.509h.1a3.38 3.38 0 002.965 1.63c2.1 0 4.121-1.729 4.121-5.376 0-3.162-1.63-5.178-
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00.775-.787v-.073a.781.781 0 00-.81-.84zm4.022 1.818v1.818h-1.63v.86h1.63v6.423a3.953
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1.976 1.848 1.848 0 01-1.818-2.115c0-2.49 2.777-2.777 4.5-2.777v2.2zm4.022
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2.757 0 00-2.957 2.541q-.006.073-.007.147c0 1.245.988 2.115 2.391 2.777s1.838 1.255
1.838 2.312a1.951 1.951 0 01-2.2 1.917 3.37 3.37 0 01-1.976-.672l-.385.86z"/></symbol>
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00-.978 3.453v.573H0v.861h1.438v9.312H2.4zm7.3-10.358c-2.3 0-4.313 1.819-4.313 5.37 0
3.355 1.819 5.184 4.128 5.184 2.113 0 4.313-1.536 4.313-5.282-.007-3.315-1.739-5.272-
4.135-5.272zm-.1.861c2.4 0 3.267 2.592 3.267 4.411 0 2.3-1.252 4.509-3.267 4.509s-
3.267-2.211-3.267-4.509c-.005-2.015.967-4.411 3.267-4.411zm6.622 9.5h.978v-6.624c.264-
1.536 1.135-2.758 2.572-2.758a.724.724 0 01.381.1v-.981a.724.724 0 00-.381-.1 2.934
2.934 0 00-2.69 2.113l-.1-1.956h-.863l.1 2.876v7.326zm9.879 0h.978v-6.527h1.819c1.819.1
2.69.978 3.071 2.934a26.409 26.409 0 00.861 3.551h.97a29.344 29.344 0 01-.978-
3.746c-.284-1.731-.978-2.778-2.113-3.071v-.1a3.775 3.775 0 002.68-3.7 3.326 3.326 0 00-
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13.295a7.443 7.443 0 011.819-.2c2.113 0 3.453.978 3.453 3.071 0 1.956-1.34 3.169-3.453
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4.128 5.468 0 2.934 1.633 5.086 4.313 5.086a6.328 6.328 0 002.778-.577l-.2-.763a4.891
4.891 0 01-2.494.479C37.9 22.3 36.19 21.251 36.19 17.7h6.7zm-6.622-.763c.1-1.536.978-
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3.169 3.169 0 01-2.015-.675l-.381.861zM59.2 17.71a1.213 1.213 0 00.1-.577c0-1.585-.675-
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2.612 0 01-2.6 1.986 1.849 1.849 0 01-1.819-2.113c.039-2.494 2.8-2.778 4.548-
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2.494 3.267v6.24h.978v-6.455c0-3.355-2.211-3.912-3.169-3.912a3.678 3.678 0 00-1.819.479
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0 01-2.4.479c-1.819 0-3.453-1.056-3.453-4.607h6.622v-.01zm-6.622-.763c.2-1.536 1.056-
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1.956 1.956 0 001.633.675 3.756 3.756 0 001.252-.2l-.1-.763a3.286 3.286 0 01-
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14.11a.506.506 0 01.041-.211l4.147-5.621.739-2.217 1.109-.41 1.15-1.6-.411-2.795a2.621
2.621 0 012.71.492A14.32 14.32 0 009.444.025a2.485 2.485 0 013 2.053 13.982 13.982 0
011.478.206.669.669 0 01.616-.452.6.6 0 01.616.616v.164a11.891 11.891 0 012.423
1.15.585.585 0 01.492-.247.6.6 0 01.616.616.505.505 0 01-.123.37 10.569 10.569 0
011.807 2.012.76.76 0 01.287-.082.641.641 0 01.657.616.55.55 0 01-.328.534A11.474
11.474 0 0121.967 10a.246.246 0 01.164-.041.6.6 0 01.616.616.593.593 0
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3.08-.041a8.5 8.5 0 00.739-3.572h1.191c0 4.681-2.34 6.529-5.256 9.4a6.09 6.09 0 00-
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2.385h19.381V29.1zm12.528-5.752a9.34 9.34 0 01-3.983-.9 25.941 25.941 0 01-.411-
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013.367.7c.082.862.164 1.848.2 3.573l-.862.041c-.411-1.438-1.067-3.2-3.162-3.2a2.2 2.2
0 00-2.341 2.341c0 3.9 7.145 3.08 7.145 8.171.005 2.414-2.172 4.508-5.374
4.508zm11.7-.164a5.527 5.527 0 01-1.519-.287v3.859c0 1.4.164 1.52 2.053 1.684v.78h-
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4.352 6.076 6.076 0 01-5.542 6.161zm.534-8.993a4.655 4.655 0 00-2.053.78v6.077a2.827
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1.6-.247 1.6-1.724V16c0-1.6-.123-1.6-1.478-1.766v-.7a25.325 25.325 0 003.572-.9v7.8c0
1.478.123 1.6 1.561 1.724v.821zm-2.709-12.524a1.417 1.417 0 010-2.833 1.417 1.417 0 110

2.833zm15.275 12.524h-4.845v-.821c1.15-.123 1.314-.247 1.314-1.561v-4.024c0-1.478-.657-2.382-1.889-2.382a3.857 3.857 0 00-2.3 1.15V20.6c0 1.314.124 1.438 1.273 1.561v.821h-5.01v-.824c1.4-.123 1.6-.247 1.6-1.561v-4.722c0-1.4-.082-1.478-1.314-1.643v-.7a21.263 21.263 0 003.449-.9v1.643a6.5 6.5 0 013.285-1.6 2.891 2.891 0 013 3.162V20.6c0 1.314.206 1.438 1.438 1.561v.82zm11.7-9.773a3.339 3.339 0 01-.985 1.273l-1.191-.123a4.016 4.016 0 01.575 2.053 4.055 4.055 0 01-4.311 3.86c-.123 0-.452-.041-.739-.041a1.42 1.42 0 00-.9 1.108c0 .37.37.822 1.355.822H89.6c1.437 0 3.367.7 3.367 3 0 2.628-2.751 4.845-5.954 4.845-2.792 0-4.271-1.724-4.271-3.121 0-.9.452-1.6 2.382-3.08a2.444 2.444 0 01-1.848-2.258 6.473 6.473 0 002.176-1.6 3.433 3.433 0 01-2.135-3.161 4.235 4.235 0 014.352-4.106 5.1 5.1 0 012.382.575c1.068-.041 2.135-.164 3.121-.287zm-3.241 11.005a8.327 8.327 0 00-2.628-.247 2.379 2.379 0 00-2.546 2.3c0 1.4 1.232 2.464 3.08 2.464a2.9 2.9 0 003.2-2.71 1.922 1.922 0 00-1.106-1.807zm-2.628-10.553c-.862 0-1.848.9-1.848 2.628s.9 2.957 2.135 2.957c.9 0 1.766-.78 1.766-2.669 0-1.602-.781-2.916-2.053-2.916zm14.494 3.613c-.369.041-3.2.246-5.789.329.082 2.711.683 3.859 3.285 3.859a3.031 3.031 0 002.381-1.067l.534.739a5.125 5.125 0 01-3.7 2.094 4.527 4.527 0 01-4.6-4.845c0-3.2 2.423-5.708 4.845-5.708a3.681 3.681 0 013.613 3.655c.006.615-.118.862-.569.944zm-3.49-3.571c-.944 0-1.93 1.027-2.176 2.792l3.531-.082c.452 0 .534-.123.534-.534a2.062 2.062 0 00-1.889-2.176zm11.825 1.519a1.4 1.4 0 00-.985-.411c-.534 0-1.232.616-1.683 1.889v3.819c0 1.4.164 1.52 1.929 1.643v.821h-5.625v-.822c1.437-.123 1.56-.247 1.56-1.643v-4.64c0-1.4-.082-1.4-1.4-1.643v-.7a20.213 20.213 0 003.531-.9V15.1h.041c.7-1.355 1.724-2.422 2.71-2.422a1.364 1.364 0 011.4 1.273c0 .938-1.026 1.76-1.478 1.267z"/></symbol><symbol id="icon-springerlink" viewBox="0 0 148 30"><path d="M23.651 23.02H4.27v-1.191h1.643c.287-3.863.982-5.3 6.036-8.417H9.568c-1.15.411-2.875 2.956-2.875 4.434h-3l.041-1.232-.986.821L.123 14.4A.632.632 0 010 14.11a.506.506 0 01.041-.211l4.147-5.621.739-2.217 1.109-.41 1.15-1.6-.411-2.795a2.621 2.621 0 012.71.492A14.32 14.32 0 009.444.025a2.485 2.485 0 013 2.053 13.982 13.982 0 011.478.206.669.669 0 01.616-.452.6.6 0 01.616.616v.164a11.891 11.891 0 012.423 1.15.585.585 0 01.492-.247.6.6 0 01.616.616.505.505 0 01-.123.37 10.569 10.569 0 011.807 2.012.76.76 0 01.287-.082.641.641 0 01.657.616.55.55 0 01-.328.534A11.474 11.474 0 0121.967 10a.246.246 0 01.164-.041.6.6 0 01.616.616.593.593 0 01-.451.616c.164.862.287 1.725.369 2.628a.641.641 0 01.657.616.67.67 0 01-.616.657c0 .862-.041 1.807-.123 2.71a.664.664 0 01.575.657.64.64 0 01-.657.616h-.041c-.164.9-.328 1.806-.534 2.751h1.725v1.194zm-2.957-1.15c2.382-9.814-.411-17.615-8.007-18.519a10.043 10.043 0 01.041 1.068c0 .493-.041.9-.041.9L11.5 5.116c.041-.411.123-3.2-.863-3.818a15.523 15.523 0 01-.328 2.956L9.2 4.05a1.66 1.66 0 00-1.069-1.725l.287 2.012-.7 1.027.33.944-2.176.739-.616 1.766-3.819 5.256 1.438 1.724 1.6-1.355.369.246V16.7h.863a8.069 8.069 0 012.669-3.942l-.616-.743.9-.78.865 1.065s3.08 0 3.08-.041a8.5 8.5 0 00.739-3.572h1.191c0 4.681-2.34 6.529-5.256 9.4a6.09 6.09 0 00-2.135 3.783h13.55zM3.573 12.8a3.172 3.172 0 01-.329 1.766l-.862-.329a2.722 2.722 0 00.452-1.478zm4.721-4.562l-1.847.985L6.323 7.7l1.93-.2zM23.651 29.1H4.27v-2.385h19.381V29.1zm12.528-5.752a9.34 9.34 0 01-3.983-.925.941 25.941 0 01-.411-3.983l.945-.165c.534 2.012 1.273 3.983 3.736 3.983a2.524 2.524 0 002.751-2.669c0-4.229-7.021-3.284-7.021-8.171 0-2.217 1.807-4.229 5.01-4.229a10.275 10.275 0 013.367.7c.082.862.164 1.848.2 3.573l-.862.041c-.411-1.438-1.067-3.2-3.162-3.2a2.2 2.2 0 00-2.341 2.341c0 3.9 7.145 3.08 7.145 8.171.005 2.414-2.172 4.508-5.374 4.508zm11.7-.164a5.527 5.527 0 01-1.519-.287v3.859c0 1.4.164 1.52 2.053 1.684v.78h-5.787v-.78c1.478-.164 1.6-.287 1.6-1.684V15.793c0-1.437-.041-1.478-1.437-1.6v-.7a27.136 27.136 0 003.572-1.027v1.56l2.217-1.15a1.668 1.668 0 01.862-.205 4.116 4.116 0 013.983 4.352 6.076 6.076 0 01-5.542 6.161zm.534-8.993a4.655 4.655 0 00-2.053.78v6.077a2.827 2.827 0 002.094.862c1.191 0 2.751-.9 2.751-3.982.002-2.587-1.23-3.737-2.79-3.737zm12.81 1.027a1.1 1.1 0 00-.985-.411c-.534 0-1.191.616-1.643 1.889v3.819c0 1.4.164 1.52 1.93 1.643v.821h-5.582v-.821c1.4-.123 1.561-.247 1.561-1.643v-4.64c0-1.4-.123-1.4-1.4-1.643v-.7a21.774 21.774 0 003.49-.9V15.1h.041c.739-1.355 1.766-2.422 2.71-2.422a1.336 1.336 0 011.4 1.273c0 .938-.985 1.76-1.52 1.267zm7.844 7.761h-5.254v-.821c1.4-.123 1.6-.247 1.6-1.561v-4.024c0-1.478-.123-1.6-1.478-1.766v-.7a25.325 25.325 0 003.572-.9v7.8c0 1.478.123 1.6 1.561 1.724v.821zm-2.709-12.524a1.417 1.417 0 010-2.833 1.417 1.417 0 110 2.833zm15.275 12.524h-4.845v-.821c1.15-.123 1.314-.247 1.314-1.561v-4.024c0-1.478-.657-2.382-1.889-2.382a3.857 3.857 0 00-2.3 1.15V20.6c0 1.314.124 1.438 1.273 1.561v.821h-5.01v-.824c1.4-.123 1.6-.247 1.6-1.561v-4.722c0-1.4-.082-1.478-1.314-1.643v-.7a21.263 21.263 0 003.449-.9v1.643a6.5 6.5 0 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1.027v4.188h-1.15V8.156h1.15v9.526a11.5 11.5 0 01.862-1.027l3.449-3.778h1.4l-4.024
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1.46 1.53 6.36 6.36 0 01-.73 0V3.3h.76c1.19 0 1.42.68 1.42 1.78zm-6.68 6.6v-2h-
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1.72V1.35H98.8v7c0 2.46 1.19 3.56 3.87 3.56s4-1.25 4-3.93zm-11.4-4.54h2V1.35h-
7v2.11h2.32v8.21h2.67V3.46h.01zm-7.85 8.2h2.76L87.72 1.34h-4L81.2 11.66h2.62L84.2
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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0.191887455 0"/></filter><filter width="170%" height="171.1%" id="m"
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.9%"
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="135.2%"
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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0.191887455 0"/></filter><filter width="175%" height="175%" id="i"
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in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)"
transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-
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60h59.1"/><path opacity=".242" fill-opacity=".707" enable-background="new" d="M1085.5
377.3h42.5l-21.2 21.3"/><path d="M1085.6 377.3l42.3 42.8h-42.3"/><path d="M1127.7
419.9l20 20h-20"/><path d="M-154.1-248.5l27 26.5h-27" filter="url(#d)"
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d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28"
filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073"
d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19"
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d="M943 405.3l59.4.1-29.6 29.8"/><path d="M-213.5-308.4l59.1 60h-59.1" filter="url(#c)" transform="rotate(180 150.533 64.5)"/><path fill-opacity=".09" d="M514.566 437.4l-59.1-60h59.1"/><path opacity=".242" fill-opacity=".707" enable-background="new" d="M1085.5 377.3h42.5l-21.2 21.3"/><path d="M1085.6 377.3l42.3 42.8h-42.3"/><path d="M1127.7 419.9l20 20h-20"/><path d="M-154.1-248.5l27 26.5h-27" filter="url(#d)" transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914 463.866l-27-26.5h27"/><g opacity=".313"><path d="M178.4 564l19.1 18.8h-19.1" filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53" d="M515.008 437.424l26.8-.212-13.506 13.505"/></g><path opacity=".16" enable-background="new" d="M455.6 377.6l59.4.1-29.6 29.8"/><path d="M137.5-281.1l29.7 29.2h-29.7" filter="url(#f)" transform="rotate(180 486.862 76.365)"/><path fill-opacity=".073" d="M836.224 433.83l-29.7-29.2h29.7"/><g opacity=".359"><path d="M470.4 530.6l21 20.3h-21" filter="url(#g)" transform="rotate(-45 486.862 61.764)"/><path fill-opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-opacity=".276" d="M720.5 404.9l-28-28h28"/><g opacity=".488"><path d="M-.9 484l20 20h-20" filter="url(#i)" transform="rotate(-45 216.435 -406.437)"/><path fill-opacity=".43" d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28" filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073" d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19"

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0.191887455 0"/></filter><filter width="125.4%" height="125%" id="n"
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0.191887455 0"/></filter><filter width="170%" height="171.1%" id="m"
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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y="-35.2%" x="-31.4%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2"
dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.9%"
height="175%" id="k" filterUnits="objectBoundingBox" y="-52.5%" x="-50%"><feOffset
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
<feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/>
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y="-37.5%" x="-33.9%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2"
dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="135.2%"
height="134.9%" id="a" filterUnits="objectBoundingBox" y="-24.4%" x="-22.3%"><feOffset
result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
<feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0.191887455 0"/></filter><filter width="175%" height="175%" id="i"
filterUnits="objectBoundingBox" y="-52.5%" x="-47.5%"><feOffset
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="171.3%"
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.5%"
height="180%" id="e" filterUnits="objectBoundingBox" y="-56%" x="-49.7%"><feOffset
result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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transform="rotate(180 772.3 55.5)"/><path fill-opacity=".107" d="M1128 419.9l-42.5-
43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)"
transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-
59.1-59.9h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new"
d="M943 405.3l59.4.1-29.6 29.8"/><path d="M-213.5-308.4l59.1 60h-59.1" filter="url(#c)"
transform="rotate(180 150.533 64.5)"/><path fill-opacity=".09" d="M514.566 437.4l-59.1-
60h59.1"/><path opacity=".242" fill-opacity=".707" enable-background="new" d="M1085.5
377.3h42.5l-21.2 21.3"/><path d="M1085.6 377.3l42.3 42.8h-42.3"/><path d="M1127.7
419.9l20 20h-20"/><path d="M-154.1-248.5l27 26.5h-27" filter="url(#d)"
transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914
463.866l-27-26.5h27"/><g opacity=".313"><path d="M178.4 564l19.1 18.8h-19.1"
filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53"
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530.6l21 20.3h-21" filter="url(#g)" transform="rotate(-45 486.862 61.764)"/><path fill-
opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-
327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-
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20" filter="url(#i)" transform="rotate(-45 216.435 -406.437)"/><path fill-opacity=".43"
d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28"
filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073"
d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19"
filter="url(#k)" transform="rotate(-45 243.935 -377.437)"/><path fill-opacity=".43"
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108.09)"/><path fill-opacity=".073" d="M867.16 465.88l-30.3-29.8h30.3"/><g
opacity=".453"><path d="M500.8 561.5l21.5 21.1h-21.5" filter="url(#m)"
transform="rotate(-45 517.492 93.077)"/><path fill-opacity=".43" d="M836.914
436.105l30.123-.283-15.203 15.203"/></g><path d="M-153.6-308.4l59.1 60h-59.1"
filter="url(#n)" transform="rotate(180 210.467 64.5)"/><path fill-opacity=".107"
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background="new" d="M514.6 377.8l59.5.1-29.7 29.8"/><path d="M612.6-285.8l46 46.9h-46"
filter="url(#o)" transform="rotate(180 970.07 80.547)"/><path fill-opacity=".107"
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background="new" d="M1280.7 400.1l47.1.1-23.5 23.6"/><path d="M942.8 405l59.1 59.9h-
59.1m-428.2-87.5l59 60h-59"/></symbol><symbol id="icon-darkred" viewBox="352 376.9 1300

89"><filter width="155.5%" height="156.6%" id="d" filterUnits="objectBoundingBox"
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filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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0.191887455 0"/></filter><filter width="132.6%" height="132%" id="o"
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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0.191887455 0"/></filter><filter width="170%" height="171.1%" id="m"
filterUnits="objectBoundingBox" y="-49.8%" x="-44.3%"><feOffset
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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0.191887455 0"/></filter><filter width="175%" height="175%" id="i"
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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height="173.7%" id="g" filterUnits="objectBoundingBox" y="-51.6%" x="-45.1%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><filter width="150.5%" height="151.4%" id="f" filterUnits="objectBoundingBox" y="-36%" x="-32%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.5%" height="180%" id="e" filterUnits="objectBoundingBox" y="-56%" x="-49.7%"><feOffset 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377.3h42.5l-21.2 21.3"/><path d="M1085.6 377.3l42.3 42.8h-42.3"/><path d="M1127.7 419.9l20 20h-20"/><path d="M-154.1-248.5l27 26.5h-27" filter="url(#d)" transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914 463.866l-27-26.5h27"/><g opacity=".313"><path d="M178.4 564l19.1 18.8h-19.1" filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53" d="M515.008 437.424l26.8-.212-13.506 13.505"/></g><path opacity=".16" enable-background="new" d="M455.6 377.6l59.4.1-29.6 29.8"/><path d="M137.5-281.1l29.7 29.2h-29.7" filter="url(#f)" transform="rotate(180 486.862 76.365)"/><path fill-opacity=".073" d="M836.224 433.83l-29.7-29.2h29.7"/><g opacity=".359"><path d="M470.4 530.6l21 20.3h-21" filter="url(#g)" transform="rotate(-45 486.862 61.764)"/><path fill-opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-opacity=".276" d="M720.5 404.9l-28-28h28"/><g opacity=".488"><path d="M-.9 484l20 20h-20" filter="url(#i)" transform="rotate(-45 216.435 -406.437)"/><path fill-opacity=".43" d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28" filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073" d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19" filter="url(#k)" transform="rotate(-45 243.935 -377.437)"/><path fill-opacity=".43" d="M720.244 405.523l27.577.707-13.434 13.435"/></g><path d="M692.5 376.9l29 29h-29"/><path d="M167.8-249.7l30.3 29.8h-30.3" filter="url(#l)" transform="rotate(180 517.48 108.09)"/><path fill-opacity=".073" d="M867.16 465.88l-30.3-29.8h30.3"/><g opacity=".453"><path d="M500.8 561.5l21.5 21.1h-21.5" filter="url(#m)" transform="rotate(-45 517.492 93.077)"/><path fill-opacity=".43" d="M836.914 436.105l30.123-.283-15.203 15.203"/></g><path d="M-153.6-308.4l59.1 60h-59.1" filter="url(#n)" transform="rotate(180 210.467 64.5)"/><path 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width="125.4%" height="125%" x="-16.1%" y="-17.5%" filterUnits="objectBoundingBox" id="c"><feOffset result="shadowOffsetOuter1" dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1" stdDeviation="2" in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha" result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/><feColorMatrix values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/></filter><filter width="125.4%" height="125%" x="-16.1%" y="-17.5%" filterUnits="objectBoundingBox" id="b"><feOffset result="shadowOffsetOuter1" dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1"

stdDeviation="2" in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha"
result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/><feColorMatrix
values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/>
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in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha" result="shadowBlurOuter1"
operator="out" in="shadowBlurOuter1"/><feColorMatrix values="0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/></filter><filter width="125.4%"
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result="shadowBlurOuter1" stdDeviation="2" in="shadowOffsetOuter1"/><feComposite
in2="SourceAlpha" result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/>
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in="shadowBlurOuter1"/></filter><filter width="170%" height="171.1%" x="-44.3%"
y="-49.8%" filterUnits="objectBoundingBox" id="m"><feOffset result="shadowOffsetOuter1"
dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1"
stdDeviation="2" in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha"
result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/><feColorMatrix
values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0" in="shadowBlurOuter1"/></filter>
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dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1" stdDeviation="2"
in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha" result="shadowBlurOuter1"
operator="out" in="shadowBlurOuter1"/><feColorMatrix values="0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/></filter><filter width="178.9%"
height="175%" x="-50%" y="-52.5%" filterUnits="objectBoundingBox" id="k"><feOffset
result="shadowOffsetOuter1" dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur
result="shadowBlurOuter1" stdDeviation="2" in="shadowOffsetOuter1"/><feComposite
in2="SourceAlpha" result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/>
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filterUnits="objectBoundingBox" id="j"><feOffset result="shadowOffsetOuter1" dy="-3"
dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1" stdDeviation="2"
in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha" result="shadowBlurOuter1"
operator="out" in="shadowBlurOuter1"/><feColorMatrix values="0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/></filter><filter width="135.2%"
height="134.9%" x="-22.3%" y="-24.4%" filterUnits="objectBoundingBox" id="a"><feOffset
result="shadowOffsetOuter1" dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur
result="shadowBlurOuter1" stdDeviation="2" in="shadowOffsetOuter1"/><feComposite
in2="SourceAlpha" result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/>
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in="shadowBlurOuter1"/></filter><filter width="175%" height="175%" x="-47.5%"
y="-52.5%" filterUnits="objectBoundingBox" id="i"><feOffset result="shadowOffsetOuter1"
dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1"
stdDeviation="2" in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha"
result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/><feColorMatrix
values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0" in="shadowBlurOuter1"/></filter>
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dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1" stdDeviation="2"
in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha" result="shadowBlurOuter1"
operator="out" in="shadowBlurOuter1"/><feColorMatrix values="0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/></filter><filter width="171.3%"
height="173.7%" x="-45.1%" y="-51.6%" filterUnits="objectBoundingBox" id="g"><feOffset
result="shadowOffsetOuter1" dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur
result="shadowBlurOuter1" stdDeviation="2" in="shadowOffsetOuter1"/><feComposite
in2="SourceAlpha" result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/>
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</filter><filter width="150.5%" height="151.4%" x="-32%" y="-36%"
filterUnits="objectBoundingBox" id="f"><feOffset result="shadowOffsetOuter1" dy="-3"
dx="-2" in="SourceAlpha"/><feGaussianBlur result="shadowBlurOuter1" stdDeviation="2"
in="shadowOffsetOuter1"/><feComposite in2="SourceAlpha" result="shadowBlurOuter1"
operator="out" in="shadowBlurOuter1"/><feColorMatrix values="0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0.191887455 0" in="shadowBlurOuter1"/></filter><filter width="178.5%"
height="180%" x="-49.7%" y="-56%" filterUnits="objectBoundingBox" id="e"><feOffset
result="shadowOffsetOuter1" dy="-3" dx="-2" in="SourceAlpha"/><feGaussianBlur
result="shadowBlurOuter1" stdDeviation="2" in="shadowOffsetOuter1"/><feComposite
in2="SourceAlpha" result="shadowBlurOuter1" operator="out" in="shadowBlurOuter1"/>

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transform="rotate(180 772.3 55.5)"/><path fill-opacity=".107" d="M776.5 47L734
4h42.6"/></g><path d="M591.3 32.1L650.4 92h-59.1"/><path d="M625.3 92.1l59.1 59.9h-
59.1" filter="url(#b)" transform="rotate(180 637.825 92.033)"/><path fill-
opacity=".107" d="M650.35 91.966l-59.1-59.9h59.1"/><path opacity=".266" fill-
opacity=".707" enable-background="new" d="M591.5 32.4l59.4.1-29.6 29.8"/><path d="M138
64.5l59.1 60H138" filter="url(#c)" transform="rotate(180 150.533 64.5)"/><path fill-
opacity=".09" d="M163.066 64.5l-59.1-60h59.1"/><path d="M163.1 4.5l59 60h-59"/><path
opacity=".242" fill-opacity=".707" enable-background="new" d="M734 4.4l42.5.1-21.2
21.2"/><path d="M734.1 4.4l42.3 42.9h-42.3"/><path d="M776.2 47l20 20h-20"/><path
d="M197.4 124.4l27 26.5h-27" filter="url(#d)" transform="rotate(180 193.907 107.683)"/>
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d="M193.5 51.8l19.2 18.7h-19.2" filter="url(#e)" transform="rotate(-45 193.913
94.39)"/><path fill-opacity=".53" d="M163.505 64.566l26.8-.353-13.577 13.576"/></g>
<path opacity=".16" enable-background="new" d="M104.1 4.7l59.4.1-29.6 29.8"/><path
d="M489 91.8l29.7 29.2H489" filter="url(#f)" transform="rotate(180 486.862 76.365)"/>
<path fill-opacity=".073" d="M484.724 60.93l-29.7-29.2h29.7"/><g opacity=".359"><path
d="M485.5 18.4l21.1 20.3h-21.1" filter="url(#g)" transform="rotate(-45 486.862
61.764)"/><path fill-opacity=".53" d="M455.236 32.064l29.274-.566-14.92 14.92"/></g>
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transform="rotate(180 193.5 38.5)"/><path fill-opacity=".276" d="M369 32L341 4h28"/><g
opacity=".488"><path d="M14.2-28.2l20 20h-20" filter="url(#i)" transform="rotate(-45
216.435 -406.437)"/><path fill-opacity=".43" d="M340.887 4.02h28.284l-14.14 14.14"/>
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20h-19" filter="url(#k)" transform="rotate(-45 243.935 -377.437)"/><path fill-
opacity=".43" d="M368.74 32.665l27.578.707-13.435 13.435"/></g><path d="M519.3
123.2l30.3 29.8h-30.3" filter="url(#l)" transform="rotate(180 517.48 108.09)"/><path
fill-opacity=".073" d="M515.66 92.98l-30.3-29.8h30.3"/><g opacity=".453"><path d="M516
49.3l21.4 21.1H516" filter="url(#m)" transform="rotate(-45 517.492 93.077)"/><path
fill-opacity=".43" d="M485.482 63.177l30.052-.212-15.132 15.132"/></g><path d="M197.9
64.5l59.1 60h-59.1" filter="url(#n)" transform="rotate(180 210.467 64.5)"/><path fill-
opacity=".107" d="M223.034 64.5l-59.1-60h59.1"/><path opacity=".266" fill-
opacity=".707" enable-background="new" d="M163.1 4.9l59.5.1-29.7 29.8"/><path d="M964.1
87.1l46 46.9h-46" filter="url(#o)" transform="rotate(180 970.07 80.547)"/><path fill-
opacity=".107" d="M976.04 73.994l-46-46.9h46"/><path opacity=".137" fill-opacity=".707"
enable-background="new" d="M929.2 27.2l47.1.1-23.5 23.6"/></symbol><symbol id="icon-
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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0.191887455 0"/></filter><filter width="125.4%" height="125%" id="c"
filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset
result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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0.191887455 0"/></filter><filter width="125.4%" height="125%" id="b"
filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset
result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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0.191887455 0"/></filter><filter width="132.6%" height="132%" id="o"
filterUnits="objectBoundingBox" y="-22.4%" x="-20.6%"><feOffset
result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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0.191887455 0"/></filter><filter width="125.4%" height="125%" id="n"
filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset
result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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0.191887455 0"/></filter><filter width="170%" height="171.1%" id="m"

filterUnits="objectBoundingBox" y="-49.8%" x="-44.3%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><filter width="149.5%" height="150.3%" id="l" filterUnits="objectBoundingBox" y="-35.2%" x="-31.4%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.9%" height="175%" id="k" filterUnits="objectBoundingBox" y="-52.5%" x="-50%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><filter width="153.6%" height="153.6%" id="j" filterUnits="objectBoundingBox" y="-37.5%" x="-33.9%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="135.2%" height="134.9%" id="a" filterUnits="objectBoundingBox" y="-24.4%" x="-22.3%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><filter width="175%" height="175%" id="i" filterUnits="objectBoundingBox" y="-52.5%" x="-47.5%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><filter width="153.6%" height="153.6%" id="h" filterUnits="objectBoundingBox" y="-37.5%" x="-33.9%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="171.3%" height="173.7%" id="g" filterUnits="objectBoundingBox" y="-51.6%" x="-45.1%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><filter width="150.5%" height="151.4%" id="f" filterUnits="objectBoundingBox" y="-36%" x="-32%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.5%" height="180%" id="e" filterUnits="objectBoundingBox" y="-56%" x="-49.7%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/></filter><g opacity=".756"><path d="M416.6-308.9l42.5 43h-42.6" filter="url(#a)" transform="rotate(180 772.3 55.5)"/><path fill-opacity=".107" d="M1128 419.9l-42.5-43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)" transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-59.1-59.9h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new" d="M943 405.3l59.4.1-29.6 29.8"/><path d="M-213.5-308.4l59.1 60h-59.1" filter="url(#c)" transform="rotate(180 150.533 64.5)"/><path fill-opacity=".09" d="M514.566 437.4l-59.1-60h59.1"/><path opacity=".242" fill-opacity=".707" enable-background="new" d="M1085.5 377.3h42.5l-21.2 21.3"/><path d="M1085.6 377.3l42.3 42.8h-42.3"/><path d="M1127.7 419.9l20 20h-20"/><path d="M-154.1-248.5l27 26.5h-27" filter="url(#d)" transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914 463.866l-27-26.5h27"/><g opacity=".313"><path d="M178.4 564l19.1 18.8h-19.1" filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53" d="M515.008 437.424l26.8-.212-13.506 13.505"/></g><path opacity=".16" enable-

background="new" d="M455.6 377.6l59.4.1-29.6 29.8"/><path d="M137.5-281.1l29.7 29.2h-29.7" filter="url(#f)" transform="rotate(180 486.862 76.365)"/><path fill-opacity=".073" d="M836.224 433.83l-29.7-29.2h29.7"/><g opacity=".359"><path d="M470.4 530.6l21 20.3h-21" filter="url(#g)" transform="rotate(-45 486.862 61.764)"/><path fill-opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-opacity=".276" d="M720.5 404.9l-28-28h28"/><g opacity=".488"><path d="M-.9 484l20 20h-20" filter="url(#i)" transform="rotate(-45 216.435 -406.437)"/><path fill-opacity=".43" d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28" filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073" d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19" filter="url(#k)" transform="rotate(-45 243.935 -377.437)"/><path fill-opacity=".43" d="M720.244 405.523l27.577.707-13.434 13.435"/></g><path d="M692.5 376.9l29 29h-29"/><path d="M167.8-249.7l30.3 29.8h-30.3" filter="url(#l)" transform="rotate(180 517.48 108.09)"/><path fill-opacity=".073" d="M867.16 465.88l-30.3-29.8h30.3"/><g opacity=".453"><path d="M500.8 561.5l21.5 21.1h-21.5" filter="url(#m)" transform="rotate(-45 517.492 93.077)"/><path fill-opacity=".43" d="M836.914 436.105l30.123-.283-15.203 15.203"/></g><path d="M-153.6-308.4l59.1 60h-59.1" filter="url(#n)" transform="rotate(180 210.467 64.5)"/><path fill-opacity=".107" d="M574.534 437.4l-59.1-60h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new" d="M514.6 377.8l59.5.1-29.7 29.8"/><path d="M612.6-285.8l46 46.9h-46" filter="url(#o)" transform="rotate(180 970.07 80.547)"/><path fill-opacity=".107" d="M1327.54 446.894l-46-46.9h46"/><path opacity=".137" fill-opacity=".707" enable-background="new" d="M1280.7 400.1l47.1.1-23.5 23.6"/><path d="M942.8 405l59.1 59.9h-59.1m-428.2-87.5l59 60h-59"/></symbol><symbol id="icon-lightblue" viewBox="352 376.9 1300 89"><filter width="155.5%" height="156.6%" id="d" filterUnits="objectBoundingBox" y="-39.6%" x="-35.2%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="125.4%" height="125%" id="c" filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="125.4%" height="125%" id="b" filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="132.6%" height="132%" id="o" filterUnits="objectBoundingBox" y="-22.4%" x="-20.6%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="125.4%" height="125%" id="n" 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0.191887455 0"/></filter><filter width="175%" height="175%" id="i"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)"
transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-
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26.5h-27" filter="url(#d)" transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914 463.866l-27-26.5h27"/><g opacity=".313"><path d="M178.4 564l19.1 18.8h-19.1" filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53" d="M515.008 437.424l26.8-.212-13.506 13.505"/></g><path opacity=".16" enable-background="new" d="M455.6 377.6l59.4.1-29.6 29.8"/><path d="M137.5-281.1l29.7 29.2h-29.7" filter="url(#f)" transform="rotate(180 486.862 76.365)"/><path fill-opacity=".073" d="M836.224 433.83l-29.7-29.2h29.7"/><g opacity=".359"><path d="M470.4 530.6l21 20.3h-21" filter="url(#g)" transform="rotate(-45 486.862 61.764)"/><path fill-opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-opacity=".276" d="M720.5 404.9l-28-28h28"/><g opacity=".488"><path d="M-.9 484l20 20h-20" filter="url(#i)" transform="rotate(-45 216.435 -406.437)"/><path fill-opacity=".43" d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28" filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073" d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19" filter="url(#k)" transform="rotate(-45 243.935 -377.437)"/><path fill-opacity=".43" d="M720.244 405.523l27.577.707-13.434 13.435"/></g><path d="M692.5 376.9l29 29h-29"/><path d="M167.8-249.7l30.3 29.8h-30.3" filter="url(#l)" transform="rotate(180 517.48 108.09)"/><path fill-opacity=".073" d="M867.16 465.88l-30.3-29.8h30.3"/><g opacity=".453"><path d="M500.8 561.5l21.5 21.1h-21.5" filter="url(#m)" transform="rotate(-45 517.492 93.077)"/><path fill-opacity=".43" d="M836.914 436.105l30.123-.283-15.203 15.203"/></g><path d="M-153.6-308.4l59.1 60h-59.1" filter="url(#n)" transform="rotate(180 210.467 64.5)"/><path fill-opacity=".107" d="M574.534 437.4l-59.1-60h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new" d="M514.6 377.8l59.5.1-29.7 29.8"/><path d="M612.6-285.8l46 46.9h-46" filter="url(#o)" transform="rotate(180 970.07 80.547)"/><path fill-opacity=".107" d="M1327.54 446.894l-46-46.9h46"/><path opacity=".137" fill-opacity=".707" enable-background="new" d="M1280.7 400.1l47.1.1-23.5 23.6"/><path d="M942.8 405l59.1 59.9h-59.1m-428.2-87.5l59 60h-59"/></symbol><symbol id="icon-lightgrey" viewBox="352 376.9 1300 89"><filter width="155.5%" height="156.6%" id="d" filterUnits="objectBoundingBox" y="-39.6%" x="-35.2%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"

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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="135.2%"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.5%"
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43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)"
transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-
59.1-59.9h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new"
d="M943 405.3l59.4.1-29.6 29.8"/><path d="M-213.5-308.4l59.1 60h-59.1" filter="url(#c)"
transform="rotate(180 150.533 64.5)"/><path fill-opacity=".09" d="M514.566 437.4l-59.1-
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filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53"
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d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28"
filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073"
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filter="url(#o)" transform="rotate(180 970.07 80.547)"/><path fill-opacity=".107"
d="M1327.54 446.894l-46-46.9h46"/><path opacity=".137" fill-opacity=".707" enable-
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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0.191887455 0"/></filter><filter width="132.6%" height="132%" id="o"
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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transform="rotate(180 772.3 55.5)"/><path fill-opacity=".107" d="M1128 419.9l-42.5-43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)" transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-59.1-59.9h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new" d="M943 405.3l59.4.1-29.6 29.8"/><path d="M-213.5-308.4l59.1 60h-59.1" filter="url(#c)" transform="rotate(180 150.533 64.5)"/><path fill-opacity=".09" d="M514.566 437.4l-59.1-60h59.1"/><path opacity=".242" fill-opacity=".707" enable-background="new" d="M1085.5 377.3h42.5l-21.2 21.3"/><path d="M1085.6 377.3l42.3 42.8h-42.3"/><path d="M1127.7 419.9l20 20h-20"/><path d="M-154.1-248.5l27 26.5h-27" filter="url(#d)" transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914 463.866l-27-26.5h27"/><g opacity=".313"><path d="M178.4 564l19.1 18.8h-19.1" filter="url(#e)" transform="rotate(-45 193.913 94.39)"/><path fill-opacity=".53" d="M515.008 437.424l26.8-.212-13.506 13.505"/></g><path opacity=".16" enable-background="new" d="M455.6 377.6l59.4.1-29.6 29.8"/><path d="M137.5-281.1l29.7 29.2h-29.7" filter="url(#f)" transform="rotate(180 486.862 76.365)"/><path fill-opacity=".073" d="M836.224 433.83l-29.7-29.2h29.7"/><g opacity=".359"><path d="M470.4 530.6l21 20.3h-21" filter="url(#g)" transform="rotate(-45 486.862 61.764)"/><path fill-opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-opacity=".276" d="M720.5 404.9l-28-28h28"/><g opacity=".488"><path d="M-.9 484l20 20h-20" filter="url(#i)" transform="rotate(-45 216.435 -406.437)"/><path fill-opacity=".43" d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28" filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073" d="M748.5 433.9l-28-28h28"/><g opacity=".548"><path d="M27.1 513l19 20h-19" filter="url(#k)" transform="rotate(-45 243.935 -377.437)"/><path fill-opacity=".43" d="M720.244 405.523l27.577.707-13.434 13.435"/></g><path d="M692.5 376.9l29 29h-29"/><path d="M167.8-249.7l30.3 29.8h-30.3" filter="url(#l)" transform="rotate(180 517.48 108.09)"/><path fill-opacity=".073" d="M867.16 465.88l-30.3-29.8h30.3"/><g opacity=".453"><path d="M500.8 561.5l21.5 21.1h-21.5" filter="url(#m)" transform="rotate(-45 517.492 93.077)"/><path fill-opacity=".43" d="M836.914 436.105l30.123-.283-15.203 15.203"/></g><path d="M-153.6-308.4l59.1 60h-59.1" filter="url(#n)" transform="rotate(180 210.467 64.5)"/><path fill-opacity=".107" d="M574.534 437.4l-59.1-60h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new" d="M514.6 377.8l59.5.1-29.7 29.8"/><path d="M612.6-285.8l46 46.9h-46" filter="url(#o)" transform="rotate(180 970.07 80.547)"/><path fill-opacity=".107" d="M1327.54 446.894l-46-46.9h46"/><path opacity=".137" fill-opacity=".707" enable-background="new" d="M1280.7 400.1l47.1.1-23.5 23.6"/><path d="M942.8 405l59.1 59.9h-59.1m-428.2-87.5l59 60h-59"/></symbol><symbol id="icon-red" viewBox="352 376.9 1300 89"><filter width="155.5%" height="156.6%" id="d" filterUnits="objectBoundingBox" y="-39.6%" x="-35.2%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="125.4%" height="125%" id="c" filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="125.4%" height="125%" id="b" filterUnits="objectBoundingBox" y="-17.5%" x="-16.1%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="132.6%" height="132%" id="o" filterUnits="objectBoundingBox" y="-22.4%" x="-20.6%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="125.4%" height="125%" 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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
<feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0"/>
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y="-35.2%" x="-31.4%"><feOffset result="shadowOffsetOuter1" in="SourceAlpha" dx="-2"
dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.9%"
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="135.2%"
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result="shadowOffsetOuter1" in="SourceAlpha" dx="-2" dy="-3"/><feGaussianBlur
stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
<feColorMatrix in="shadowBlurOuter1" values="0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
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result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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dy="-3"/><feGaussianBlur stdDeviation="2" result="shadowBlurOuter1"
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)"
transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-
59.1-59.9h59.1"/><path opacity=".266" fill-opacity=".707" enable-background="new"
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```

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opacity=".53" d="M806.74 404.922l29.202-.495-14.85 14.85"/></g><path d="M-333.5-
327.9l28 28h-28" filter="url(#h)" transform="rotate(180 193.5 38.5)"/><path fill-
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d="M692.39 376.876h28.284l-14.142 14.142"/></g><path d="M-305.5-298.9l28 28h-28"
filter="url(#j)" transform="rotate(180 221.5 67.5)"/><path fill-opacity=".073"
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436.105l30.123-.283-15.203 15.203"/></g><path d="M-153.6-308.4l59.1 60h-59.1"
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d="M574.534 437.4l-59.1-60h59.1"/><path opacity=".266" fill-opacity=".707" enable-
background="new" d="M514.6 377.8l59.5.1-29.7 29.8"/><path d="M612.6-285.8l46 46.9h-46"
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background="new" d="M1280.7 400.1l47.1.1-23.5 23.6"/><path d="M942.8 405l59.1 59.9h-
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in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
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```

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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
result="shadowBlurOuter1" in="shadowBlurOuter1" operator="out" in2="SourceAlpha"/>
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operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
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in="shadowOffsetOuter1"/><feComposite result="shadowBlurOuter1" in="shadowBlurOuter1"
operator="out" in2="SourceAlpha"/><feColorMatrix in="shadowBlurOuter1" values="0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0.191887455 0"/></filter><filter width="178.5%"
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stdDeviation="2" result="shadowBlurOuter1" in="shadowOffsetOuter1"/><feComposite
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transform="rotate(180 772.3 55.5)"/><path fill-opacity=".107" d="M1128 419.9l-42.5-
43h42.6"/></g><path d="M273.8-280.8l59.1 59.9h-59.1" filter="url(#b)"
transform="rotate(180 637.825 92.033)"/><path fill-opacity=".107" d="M1001.85 464.866l-
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transform="rotate(180 193.907 107.683)"/><path fill-opacity=".253" d="M541.914
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727 volume 14, Article number: 728 (2013)

728 Cite this article

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<i>Fusarium graminearum</i> Schwabe is one of the most prevalent diseases of wheat
(<i>Triticum aestivum</i> L<i>.</i>) and other small grain cereals. Resistance against
the fungus is quantitative and more than 100 quantitative trait loci (QTL) have been
described. Two well-validated and highly reproducible QTL, <i>Fhb1</i> and <i>Qfhs.ifa-
5A</i> have been widely investigated, but to date the underlying genes have not been
identified.</p><h3 class="c-article__sub-heading u-h3" data-test="abstract-sub-
heading">Results</h3><p>We have investigated a gene co-expression network activated in
response to <i>F. graminearum</i> using RNA-seq data from near-isogenic lines,
harboring either the resistant or the susceptible allele for <i>Fhb1</i> and
<i>Qfhs.ifa-5A</i>. The network identified pathogen-responsive modules, which were
enriched for differentially expressed genes between genotypes or different time points
after inoculation with the pathogen. Central gene analysis identified transcripts
associated with either QTL within the network. Moreover, we present a detailed gene
expression analysis of four gene families (glucanases, NBS-LRR, WRKY transcription
factors and UDP-glycosyltransferases), which take prominent roles in the pathogen
response.</p><h3 class="c-article__sub-heading u-h3" data-test="abstract-sub-
heading">Conclusions</h3><p>A combination of a network-driven approach and differential
gene expression analysis identified genes and pathways associated with <i>Fhb1</i> and
<i>Qfhs.ifa-5A</i>. We find G-protein coupled receptor kinases and biosynthesis genes
for jasmonate and ethylene earlier induced for <i>Fhb1</i>. Similarly, we find genes
involved in the biosynthesis and metabolism of riboflavin more abundant for
<i>Qfhs.ifa-5A</i>.</p></div></div></section>
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<section aria-labelledby="Sec1"><div class="c-article-section" id="Sec1-section"><h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Sec1">Background</h2><div class="c-article-section__content" id="Sec1-content"><p>Bread wheat (<i>Triticum aestivum</i> L.) is one of the most important food crops worldwide. 20% of the human calorie and protein uptake derive from wheat. One of its most prevalent and destructive pathogens is the fungus <i>Fusarium graminearum</i> (teleomorph <i>Gibberella zeae,</i> Schwabe) [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 1" title="Cuomo CA, Guldener U, Xu JR, Trail F, Turgeon BG, Di Pietro A, Walton JD, Ma LJ, Baker SE, Rep M, Adam G, Antoniw J, Baldwin T, Calvo S, Chang Y-L, DeCaprio D, Gale KR, Gnerre S, Goswami RS, Hammond-Kosack K, Harris LJ, Hilburn K, Kennell JC, Kroken S, Magnuson JK, Mannhaupt G, Mauceli E, Mewes H-W, Mitterbauer R, Muehlbauer G, et al: The Fusarium graminearum genome reveals a link between localized polymorphism and pathogen specialization. Science. 2007, 317: 1400-1402. 10.1126/science.1143708." href="/articles/10.1186/1471-2164-14-728#ref-CR1" id="ref-link-section-d51289e593">1</a>, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 2" title="Walter S, Nicholson P, Doohan FM: Action and reaction of host and pathogen during Fusarium head blight disease. New Phytol. 2010, 185: 54-66. 10.1111/j.1469-8137.2009.03041.x." href="/articles/10.1186/1471-2164-14-728#ref-CR2" id="ref-link-section-d51289e596">2</a>]. <i>F. graminearum</i> frequently infects wheat and other small grain cereals in temperate regions throughout the world. Especially under humid weather conditions spores that have overwintered in remaining plant debris on the field reach the flowering wheat head via splash water, from where the germinating fungus penetrates the more susceptible floral tissue. The resulting disease Fusarium head blight (FHB) annually accounts for severe losses in grain yield and also quality due to the contamination with mycotoxins produced by the fungus. Among these deoxynivalenol (DON) holds a key position. DON is a potent inhibitor of protein biosynthesis and constitutes a serious threat to human and animal health in food and feed [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 3" title="Pestka JJ: Deoxynivalenol: mechanisms of action, human exposure, and toxicological relevance. Arch Toxicol. 2010, 84: 663-679. 10.1007/s00204-010-0579-8." href="/articles/10.1186/1471-2164-14-728#ref-CR3" id="ref-link-section-d51289e603">3</a>]. This has, among others, prompted the European Union to enact maximum tolerated levels in food [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 4" title="The European Commission: Commission recommendation (EC) no. 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. Off J Eur Union. 2006, 364: 5-24." href="/articles/10.1186/1471-2164-14-728#ref-CR4" id="ref-link-section-d51289e606">4</a>] and advisory levels were issued by the Food and Drug Administration in the United States. Consequently, developing high yielding and <i>F. graminearum</i> resistant varieties is of high priority for breeders. Despite its economic relevance, the genomic sequence of wheat is not yet available due to its sheer size (~ 17 Gb) and its highly repetitive nature [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 5" title="Brenchley R, Spannagl M, Pfeifer M, Barker GL, D'Amore R, Allen AM, McKenzie N, Kramer M, Kerhornou A, Bolser D, Kay S, Waite D, Trick M, Bancroft I, Gu Y, Huo N, Luo M-C, Sehgal S, Gill B, Kianian S, Anderson O, Kersey P, Dvorak J, McCombie WR, Hall A, Mayer FKX, Edwards KJ, Bevan MW, Hall N: Analysis of the bread wheat genome using whole-genome shotgun sequencing. Nature. 2012, 491: 705-710. 10.1038/nature11650." href="/articles/10.1186/1471-2164-14-728#ref-CR5" id="ref-link-section-d51289e612">5</a>, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 6" title="Paux E, Roger D, Badaeva E, Gay G, Bernard M, Sourdille P, Feuillet C: Characterizing the composition and evolution of homoeologous genomes in hexaploid wheat through BAC-end sequencing on chromosome 3B. Plant J. 2006, 48: 463-474. 10.1111/j.1365-313X.2006.02891.x." href="/articles/10.1186/1471-2164-14-728#ref-CR6" id="ref-link-section-d51289e615">6</a>]. However, a large body of publications aiming towards genetic mapping of resistance genes against <i>F. graminearum</i> has been published in the last 14 years and so far over 100 quantitative trait loci (QTL) have been described to contribute to resistance [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 7" title="Buerstmayr H, Ban T, Anderson JA: QTL mapping and marker-assisted selection for fusarium head blight resistance in wheat: a review. Plant Breed. 2009, 128: 1-26. 10.1111/j.1439-0523.2008.01550.x." href="/articles/10.1186/1471-2164-14-728#ref-CR7" id="ref-link-section-d51289e622">7</a>]. Two highly reproducible and large-effect QTL are <i>Fhb1</i> located on the short arm of chromosome 3B [<a data-track="click" data-
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track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 8" title="Waldron BL, Moreno-Sevilla B, Anderson JA, Stack RW, Frohberg RC: RFLP mapping of QTL for fusarium head blight resistance in wheat. Crop Sci. 1999, 39: 805–811. 10.2135/cropsci1999.0011183X003900030032x." href="/articles/10.1186/1471-2164-14-728#ref-CR8" id="ref-link-section-d51289e628">8] and Qfhs.ifa-5A on chromosome 5A [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 9" title="Buerstmayr H, Lemmens M, Hartl L, Doldi L, Steiner B, Stierschneider M, Ruckenbauer P: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. I. Resistance to fungal spread (Type II resistance). Theor Appl Genet. 2002, 104: 84–91. 10.1007/s001220200009." href="/articles/10.1186/1471-2164-14-728#ref-CR9" id="ref-link-section-d51289e634">9]. Depending on the genetic background both reduce disease symptoms by 20–25% and confer either type II resistance against spreading of the disease (Fhb1) or type I resistance against initial penetration (Qfhs.ifa-5A) [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 9" title="Buerstmayr H, Lemmens M, Hartl L, Doldi L, Steiner B, Stierschneider M, Ruckenbauer P: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. I. Resistance to fungal spread (Type II resistance). Theor Appl Genet. 2002, 104: 84–91. 10.1007/s001220200009." href="/articles/10.1186/1471-2164-14-728#ref-CR9" id="ref-link-section-d51289e644">9, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 10" title="Buerstmayr H, Steiner B, Hartl L, Griesser M, Angerer N, Lengauer D, Miedaner T, Schneider B, Lemmens M: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. II. Resistance to fungal penetration and spread. Theor Appl Genet. 2003, 107: 503–508. 10.1007/s00122-003-1272-6." href="/articles/10.1186/1471-2164-14-728#ref-CR10" id="ref-link-section-d51289e647">10]. Fhb1 was linked to the higher ability to enzymatically inactivate DON by glycosylation [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 11" title="Lemmens M, Scholz U, Berthiller F, Dall’Asta C, Koutnik A, Schuhmacher R, Adam G, Buerstmayr H, Mesterhazy A, Krska R, Ruckenbauer P: The ability to detoxify the mycotoxin deoxynivalenol colocalizes with a major quantitative trait locus for fusarium head blight resistance in wheat. Mol Plant-Microbe Interact. 2005, 18: 1318–1324. 10.1094/MPMI-18-1318." href="/articles/10.1186/1471-2164-14-728#ref-CR11" id="ref-link-section-d51289e653">11], but recent reports also associate the higher formation of phenylpropanoids [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 12" title="Gunnaiah R, Kushalappa AC, Duggavathi R, Fox S, Somers DJ: Integrated metabolo-proteomic approach to decipher the mechanisms by which wheat QTL (Fhb1) contributes to resistance against Fusarium graminearum. PloS one. 2012, 7: e40695-10.1371/journal.pone.0040695." href="/articles/10.1186/1471-2164-14-728#ref-CR12" id="ref-link-section-d51289e657">12] or a non-responsive susceptibility factor, WFhb1_c1[<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 13" title="Zhuang Y, Gala A, Yen Y: Identification of functional genic components of major Fusarium head blight resistance quantitative trait loci in wheat cultivar Sumai 3. Mol Plant-Microbe Interact. 2013, 26: 442–450. 10.1094/MPMI-10-12-0235-R." href="/articles/10.1186/1471-2164-14-728#ref-CR13" id="ref-link-section-d51289e663">13] with the activity of the QTL. No functional evidence has been proposed for Qfhs.ifa-5A. A donor of both QTL is the CIMMYT (http://www.cimmyt.org) derived line CM-82036, a progeny of the prominent resistance source Sumai-3. CM-82036 also encodes for multiple minor effect resistance QTL, which provide the line with a significantly higher level of resistance when compared to a near-isogenic line stacking both Fhb1 and Qfhs.ifa-5A resistance alleles in a susceptible background [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 10" title="Buerstmayr H, Steiner B, Hartl L, Griesser M, Angerer N, Lengauer D, Miedaner T, Schneider B, Lemmens M: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. II. Resistance to fungal penetration and spread. Theor Appl Genet. 2003, 107: 503–508. 10.1007/s00122-003-1272-6." href="/articles/10.1186/1471-2164-14-728#ref-CR10" id="ref-link-section-d51289e683">10, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol Plant Pathol. 2013, 14: 772–785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e686">14]. Recent years have seen multiple transcriptomic and proteomic studies investigating the F.

graminearum/wheat-interaction, which have helped developing an understanding of the general response against the fungus (reviewed in [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 2" title="Walter S, Nicholson P, Doohan FM: Action and reaction of host and pathogen during Fusarium head blight disease. New Phytol. 2010, 185: 54-66. 10.1111/j.1469-8137.2009.03041.x." href="/articles/10.1186/1471-2164-14-728#ref-CR2" id="ref-link-section-d51289e695">2]), but these did not lead to the identification of QTL-related resistance genes so far. RNA-sequencing technology is well established as an alternative to microarrays. The major obstacle for the analysis of the entire wheat transcriptome is the availability of a suitable mapping reference covering the gene space of the yet unsequenced species. Establishing the gene-space as a reference is even more challenging as the three homeologous genomes of polyploid bread wheat share a high level of sequence similarity. A recent study [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 15" title="Schreiber A, Hayden M, Forrest K, Kong S, Langridge P, Baumann U: Transcriptome-scale homoeolog-specific transcript assemblies of bread wheat. BMC Genom. 2012, 13: 492-10.1186/1471-2164-13-492." href="/articles/10.1186/1471-2164-14-728#ref-CR15" id="ref-link-section-d51289e701">15] tried to overcome these limitations by combining short reads from Illumina technology with 454 data in a two-stage assembly. The TriFLDB [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 16" title="Mochida K, Yoshida T, Sakurai T, Ogihara Y, Shinozaki K: TriFLDB: a database of clustered full-length coding sequences from Triticeae with applications to comparative grass genomics. Plant Physiol. 2009, 150: 1135-1146. 10.1104/pp.109.138214." href="/articles/10.1186/1471-2164-14-728#ref-CR16" id="ref-link-section-d51289e707">16] database collected available full-length coding sequences from wheat over the last years. Currently, efforts are underway to assemble the wheat genome entirely using chromosome arm sorting [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 17" title="Kubalakova M, Vrana J, Cihalikova J, Simkova H, Dolezel J: Flow karyotyping and chromosome sorting in bread wheat (Triticum aestivum L.). Theor Appl Genet. 2002, 104: 1362-1372. 10.1007/s00122-002-0888-2." href="/articles/10.1186/1471-2164-14-728#ref-CR17" id="ref-link-section-d51289e710">17], genotyping by sequencing [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 18" title="Poland JA, Brown PJ, Sorrells ME, Jannink JL: Development of high-density genetic maps for barley and wheat using a novel two-enzyme genotyping-by-sequencing approach. PloS one. 2012, 7: e32253-10.1371/journal.pone.0032253." href="/articles/10.1186/1471-2164-14-728#ref-CR18" id="ref-link-section-d51289e713">18] and whole genome profiling approaches [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 19" title="Philippe R, Choulet F, Paux E, van Oeveren J, Tang J, Wittenberg AH, Janssen A, van Eijk MJ, Stormo K, Alberti A, Wincker P, Akhunov E, van der Vossen E, Feuillet C: Whole genome profiling provides a robust framework for physical mapping and sequencing in the highly complex and repetitive wheat genome. BMC genom. 2012, 13: 47-" href="/articles/10.1186/1471-2164-14-728#ref-CR19" id="ref-link-section-d51289e717">19]. The most complete assembly of the T. aestivum gene space is described by the released wheat low-copy-number genome (LCG) assembly [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 5" title="Brenchley R, Spannagl M, Pfeifer M, Barker GL, D'Amore R, Allen AM, McKenzie N, Kramer M, Kerhornou A, Bolser D, Kay S, Waite D, Trick M, Bancroft I, Gu Y, Huo N, Luo M-C, Sehgal S, Gill B, Kianian S, Anderson O, Kersey P, Dvorak J, McCombie WR, Hall A, Mayer FKX, Edwards KJ, Bevan MW, Hall N: Analysis of the bread wheat genome using whole-genome shotgun sequencing. Nature. 2012, 491: 705-710. 10.1038/nature11650." href="/articles/10.1186/1471-2164-14-728#ref-CR5" id="ref-link-section-d51289e723">5], generated from 454 sequences and reference as well as progenitor genomes, which provides partial sequences of an estimated number of 94 - 96 k genes. In addition, the transcriptome of the close relative barley (Hordeum vulgare L.) comprising more than 26 k genes has been annotated on a WGS assembly and anchored to the physical map [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 20" title="The International Barley Genome Sequencing Consortium: A physical, genetic and functional sequence assembly of the barley genome. Nature. 2012, 491: 711-716." href="/articles/10.1186/1471-2164-14-728#ref-CR20" id="ref-link-section-d51289e732">20]. These data, the wheat LCG assembly and the homology to the complete barley gene space provide a novel and unique reference for RNA-profiling studies, allowing a high specificity and coverage of the transcriptome. To gain novel insights into the defense response of wheat against F. graminearum using these newly available data resources, we have sequenced the transcriptome of five

differently resistant genotypes, comprising a set of four near-isogenic lines (NILs) harboring either, both or none of the resistance alleles of Fhb1 and Qhfs.ifa-5A in the susceptible background of the German spring wheat cultivar Remus and the highly resistant QTL-donor line CM-82036. While most of the existing, microarray-based analyses aimed at analyzing single genes, we here provide a transcriptome-wide approach and focus on investigating the interaction of genes. Several studies have demonstrated the power of co-expression networks for detecting groups of genes that react in a coordinated effort against pathogen response, e.g. in cucumber and rice [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 21" title="Adhikari BN, Savory EA, Vaillancourt B, Childs KL, Hamilton JP, Day B, Buell CR: Expression profiling of Cucumis sativus in response to infection by Pseudoperonospora cubensis. PloS one. 2012, 7: e34954-10.1371/journal.pone.0034954." href="/articles/10.1186/1471-2164-14-728#ref-CR21" id="ref-link-section-d51289e747">21, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 22" title="Bagnaresi P, Biselli C, Orru L, Urso S, Crispino L, Abbruscato P, Piffanelli P, Lupotto E, Cattivelli L, Vale G: Comparative transcriptome profiling of the early response to Magnaporthe oryzae in durable resistant vs susceptible rice (Oryza sativa L.) genotypes. PloS one. 2012, 7: e51609-10.1371/journal.pone.0051609." href="/articles/10.1186/1471-2164-14-728#ref-CR22" id="ref-link-section-d51289e750">22]. In the present study we introduce a network-driven approach, which led to the identification of groups of genes that form functional clusters of co-expressed genes. Additionally, we screened for single genes that occupy central positions within the newly established network (e.g. hub genes). We find that these putative key genes in the response to F. graminearum are members of prominent pathogenesis-related gene families. We further investigate differential expression patterns observed for the glucanase, nucleotide-binding site leucine-rich repeat (NBS-LRR), WRKY and UDP-glycosyltransferase (UGT) gene families, which hold relevant positions in our analysis. </section><section aria-labelledby="Sec2"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Sec2">Results</h2> <h3 class="c-article__sub-heading u-h3" id="Sec3">Data harvesting, processing and quality control</h3> We extracted RNA from spike tissue of five different wheat genotypes that were treated with a F. graminearum spore suspension or mock 30 and 50 hours after inoculation (hai). All lines showed distinct levels of resistance after point inoculation in green house trials [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 10" title="Buerstmayr H, Steiner B, Hartl L, Griesser M, Angerer N, Lengauer D, Miedaner T, Schneider B, Lemmens M: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. II. Resistance to fungal penetration and spread. Theor Appl Genet. 2003, 107: 503-508. 10.1007/s00122-003-1272-6." href="/articles/10.1186/1471-2164-14-728#ref-CR10" id="ref-link-section-d51289e772">10, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol Plant Pathol. 2013, 14: 772-785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e775">14]. The lines comprised a set of four NILs that harbor either of the F. graminearum-resistance QTL Fhb1 (NIL2, moderately resistant) or Qfhs.ifa-5A (NIL3, moderately resistant), both of these QTL (NIL1, resistant) or none of them (NIL4, susceptible) in the genetic background of the F. graminearum susceptible German spring wheat cultivar Remus. These lines are at least 96% isogenic as shown with DArT markers [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol Plant Pathol. 2013, 14: 772-785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e791">14], but do contain QTL-unrelated, yet linked genes from the original QTL donor in the introgressed section. Additional samples were collected from the highly resistant QTL-donor line CM-82036, which encodes in addition to Fhb1 and Qfhs.ifa-5A for multiple minor-effect QTL. Samples were sequenced on an Illumina HiSeq2000 platform, which summed up to a total of 1,827 Gb raw sequences (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM1">1). RNA-Seq reads were compared against public wheat full-length cDNA [<a data-track="click" data-track-

action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 16" title="Mochida K, Yoshida T, Sakurai T, Ogihara Y, Shinozaki K: TriFLDB: a database of clustered full-length coding sequences from Triticeae with applications to comparative grass genomics. Plant Physiol. 2009, 150: 1135-1146. 10.1104/pp.109.138214." href="/articles/10.1186/1471-2164-14-728#ref-CR16" id="ref-link-section-d51289e804">16] to ensure the quality and coverage of genes along the entire length (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM2">2). This allowed to map reads on the LCG assembly [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 5" title="Brenchley R, Spannagl M, Pfeifer M, Barker GL, D'Amore R, Allen AM, McKenzie N, Kramer M, Kerhornou A, Bolser D, Kay S, Waite D, Trick M, Bancroft I, Gu Y, Huo N, Luo M-C, Sehgal S, Gill B, Kianian S, Anderson O, Kersey P, Dvorak J, McCombie WR, Hall A, Mayer FKX, Edwards KJ, Bevan MW, Hall N: Analysis of the bread wheat genome using whole-genome shotgun sequencing. Nature. 2012, 491: 705-710. 10.1038/nature11650." href="/articles/10.1186/1471-2164-14-728#ref-CR5" id="ref-link-section-d51289e810">5] resulting in 233,780 Cuffmerge transcripts, out of which 151,853 (65%) transcripts are expressed in all five genotypes (Table <a data-track="click" data-track-label="link" data-track-action="table anchor" href="/articles/10.1186/1471-2164-14-728#Tab1">1). To assess the progress of the disease, reads were compared to the F. graminearum transcriptome [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 23" title="Wong P, Walter M, Lee W, Mannhaupt G, Munsterkotter M, Mewes HW, Adam G, Guldener U: FGDB: revisiting the genome annotation of the plant pathogen fusarium graminearum. Nuc Acids Res. 2011, 39: D637-D639. 10.1093/nar/gkq1016." href="/articles/10.1186/1471-2164-14-728#ref-CR23" id="ref-link-section-d51289e819">23]. In average 87 k reads (0.3% from the average of total reads) were matching F. graminearum genes for samples inoculated with spore suspensions and no more than about 1.8 k reads in the mock-treated samples (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM3">3). This observation can be explained by contaminations, mapping errors or conserved domains. One particular mock treated sample (NIL2, 50 hai, replicate 3) contained an unexpected high number of reads (10.7 k reads) that matched F. graminearum genes and was therefore excluded from further analysis. While samples taken at 50 hai showed in general a higher abundance of F. graminearum-mapped reads than 30 hai samples, we could not detect significant differences between the infected lines at any time point (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM4">4). <figure><figcaption class="c-article-table__figcaption">Table 1
Mapping of RNA-seq data
</figcaption> Full size table<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-chevron-right"></use></svg> </figure> Cuffdiff [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 24" title="Trapnell C, Roberts A, Goff L, Pertea G, Kim D, Kelley DR, Pimentel H, Salzberg SL, Rinn JL, Pachter L: Differential gene and transcript expression analysis of RNA-seq experiments with TopHat and cufflinks. Nat Protoc. 2012, 7: 562-578." href="/articles/10.1186/1471-2164-14-728#ref-CR24" id="ref-link-section-d51289e1038">24] was used to extract differentially expressed genes (Benjamini-Hochberg correction [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 25" title="Benjamini Y, Hochberg Y: Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Stat Methodol. 1995, 57: 289-300." href="/articles/10.1186/1471-2164-14-728#ref-CR25" id="ref-link-section-d51289e1041">25] (BH); p < 0.1; see Methods). As the LCG contigs are in general short (average length: 714 bp) and represent only partial genes due to the high (genic) sequence redundancy in hexaploid wheat, we used the recently published barley high confidence genes (N = 26,159, [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 18" title="Poland JA, Brown PJ, Sorrells ME, Jannink JL: Development of high-density genetic maps for barley and wheat using a novel two-enzyme genotyping-by-sequencing approach. PloS one. 2012, 7: e32253-10.1371/journal.pone.0032253."

href="/articles/10.1186/1471-2164-14-728#ref-CR18" id="ref-link-section-d51289e1050">18]) to filter the previously generated fragmented Cufflinks transcripts for gene candidates. Thereby, with the barley best bidirectional hit (BBH), we were able to link 16,964 transcripts to barley genes. Mapping to barley homologs has two major impacts: It drastically reduces the number of analyzed transcripts in the analysis and also wheat-specific genes with no barley homologs may be lost. Moreover, a differentiation between homeologous genes from different genomes is not always possible. However, the remaining transcripts have a higher quality in terms of gene calling confidence. Additionally, for these data trustworthy sets of Gene Ontology (GO) and Interpro annotations exist for analyzing the remaining transcripts. Overall these sets comprised 9,776 genes with GO annotations and 14,164 genes with Interpro annotations. Therefore, we performed the subsequent enrichment analyses and network inference on the barley BBH reduced subset. <h3 class="c-article__sub-heading u-h3" id="Sec4">Genotype-specific differentially expressed genes link Fhb1 to early induction of jasmonate and ethylene biosynthesis and Qfhs.ifa-5Ato riboflavin biosynthesis and lipid binding</h3> With Cuffcompare 233 k cufflinks genes were combined and tested for differential expression by comparing F. graminearum inoculated samples with the respective mock-treated sample (FDR adjusted p-value < 0.1). Per genotype between 183,540 (CM-82036) to 196,078 (NIL2) Cufflinks genes were assembled. BBH assigned barley genes were found for 15,360 (CM-82036) to 15,797 (NIL1) Cufflinks genes. In average 8% of those genes were differentially expressed, for Cufflinks genes with BBH linkage 11–13%. To provide a more granular insight into differentially expressed genes, we analyzed common differentially expressed genes (DEG) for 30 hai and 50 hai separately. A list of all analyzed differentially expressed genes is provided in Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM5">5. The earlier sampling time point 30 hai was characterized by a pronounced response of the resistant CM-82036 (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig1">1a). From the 1,302 DEG identified in total, 289 were differentially expressed only for CM-82036 compared to 114 DEG, which were shared between all five genotypes. The group of DEG shared only between NILs 1–4 and also the number of DEG specific for each NIL comprised only few genes (10 to 41). 50 hai a large part (618) of the 2,470 DEG was significantly changed for all genotypes. At this time point, in contrast to 30 hai, all genotypes exhibited a similarly strong response in terms of DEGs (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig1">1b). Also a large group of DEG was shared between the four NILs (114) representing the response of genes in the genetic background of the susceptible recurrent parent Remus. <figure><figcaption>Figure 1</figcaption> <picture><source type="image/webp" srcset="//media.springernature.com/lw685/springer-static/image/art%3A10.1186%2F1471-2164-14-728/MediaObjects/12864_2013_Article_7140_Fig1_HTML.jpg?as=webp"></source></picture> Differentially expressed genes per line. Venn diagrams showing unique F. graminearum responsive genes at 30 hours after inoculation (hai) (a) and 50 hai (b) for the investigated genotypes (CM-82036, NIL1 (harboring both resistance QTL, Fhb1 and Qfhs.ifa-5A), NIL2 (Fhb1), NIL3 (Qhfs.ifa-5A) and NIL4 (no QTL)) as well as genes shared between them in the respective intersections. Intersections of lines sharing either of the two QTL harbor genes associated with these QTL. These are highlighted in cyan (Fhb1) or magenta (Qfhs.ifa-5A). Full size image<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-chevron-right"></use></svg> </figure> GO terms obtained via topGO [<a data-track="click" data-track-action="reference anchor"

data-track-label="link" data-test="citation-ref" aria-label="Reference 26" title="Alexa A, Rahnenführer J, Lengauer T: Improved scoring of functional groups from gene expression data by decorrelating GO graph structure. Bioinformatics. 2006, 22: 1600-1607. 10.1093/bioinformatics/btl140." href="/articles/10.1186/1471-2164-14-728#ref-CR26" id="ref-link-section-d51289e1137">26] for these contrasts represented genotype dependent defense responses (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM6">6 for 30 hai and Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM7">7 for 50 hai). Regardless of QTL all genotypes shared essential pathogenesis associated pathways at 30 hai: These included the biosynthesis of phenylpropanoids and polyamins and also genes involved in the reduction of oxidative stress and chitinases. We also found a glutamate synthase more abundant 30 hai and an amino acid transporter more abundant at 50 hai. Both may be linked to multiple pathogen-induced reactions in the primary and secondary metabolism [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 27" title="Bolton MD: Primary metabolism and plant defense–fuel for the fire. Mol Plant-Microbe Interact. 2009, 22: 487-497. 10.1094/MPMI-22-5-0487." href="/articles/10.1186/1471-2164-14-728#ref-CR27" id="ref-link-section-d51289e1146">27, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 28" title="Seifi HS, Van Bockhaven J, Angenon G, Hofte M: Glutamate metabolism in plant disease and defense: friend or foe?. Mol Plant-Microbe Interact. 2013, 26: 475-485. 10.1094/MPMI-07-12-0176-CR." href="/articles/10.1186/1471-2164-14-728#ref-CR28" id="ref-link-section-d51289e1149">28]. Moreover, an UDP-N-acetylmuramate dehydrogenase was also upregulated 30 hai, which potentially acts in biosynthesis of amino sugars used for posttranslational protein modification. 50 hai we observed additional terms related to ubiquitination and the biosynthesis of tryptophan. The response unique for CM-82036 comprised a high number of terms corresponding to signaling events and transcription factors at the early time point and also terms corresponding to the biosynthesis of trehalose and terpenoids. The response at 50 hai included UGTs, cytochrome P450 monooxygenases (CYP) and terms related to the primary metabolism involved in amino acid biosynthesis and gluconeogenesis. Genes associated with the activity of Fhb1 or Qfhs.ifa-5A should be represented by DEG shared by NILs harboring these QTL (highlighted sections in Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig1">1). In the section shared by NIL2 (resistant allele of Fhb1) and NIL1 (both QTL) and in the section shared by both NILs and CM-82036 we identified 16 genes collectively at 30 hai and 47 at 50 hai. Similarly, 26 and 60 genes were shared in lines harboring the resistance allele of Qfhs.ifa-5A (NIL1 and NIL3 containing Qfhs.ifa-5A only and optionally CM-82036). We also looked at the differentially expressed genes unique for the genotypes harboring only either of both QTL (NIL2 and NIL3), as the activity of QTL-related genes might not be similarly significantly changed at the observed time point in all lines harboring these QTL due to the different resistance levels. The specific response of the NIL2 containing Fhb1 was characterized by the early upregulation of transcription factors and biosynthesis genes for jasmonic acid (JA) and ethylene (ET). Both signaling molecules regulate defense responses in plants against biotic stresses. At 50 hai we found terms related to translation, protein folding and ribosomal protein more abundant. For transcripts shared between lines with Fhb1 we identified GO terms relating to protein secretion and signal transduction (G protein-related) at 30 hai and terms related to the metabolism of glutamine at 50 hai. Lines containing Qfhs.ifa-5A (NIL1 and NIL3) showed higher abundance of gene transcripts related to the tryptophan biosynthesis pathway already at 30 hai and for genes related to lipid binding at 50 hai. GO terms identified in the shared sections are involved in riboflavin production and ET biosynthesis (30 hai). We also found a transcript encoding a glutamate-gated ion channel (30 hai), which controls Ca²⁺-influx into the cell. Similarly to Fhb1, these sections also included terms for ribosome biogenesis and protein translation. <h3 class="c-article__sub-heading u-h3" id="Sec5">Gene co-expression network analysis identifies defense-associated modules</h3> We analyzed the co-expression data from the barley-mapped transcripts of all samples to infer a gene co-expression network specific for the observed conditions. In contrast to the detection of single DEG, this approach takes into account all 20 experimental conditions (covered by 59 samples) simultaneously and allows detecting groups of genes that show similar expression patterns in an untargeted approach. The resulting network contained 3,412 genes after filtering using the coefficient of variation. The co-expressions of these genes were then fitted against a power-law model using the WGCNA package in R [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 29"

title="Langfelder P, Horvath S: WGCNA: an R package for weighted correlation network analysis. BMC bioinformatics. 2008, 9: 559-10.1186/1471-2105-9-559." href="/articles/10.1186/1471-2164-14-728#ref-CR29" id="ref-link-section-d51289e1202">29]. We extracted eight modules (designated module A to module H) from our network, each represented by a group of genes that share similar expression patterns (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig2">2; Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM8">8). Module sizes ranged from 109 (module G) to 1,148 genes (module B), while 139 genes could not be assigned to any module. (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM9">9). <figure><figcaption>Figure 2</figcaption> <picture><source type="image/webp" srcset="//media.springernature.com/lw685/springer-static/image/art%3A10.1186%2F1471-2164-14-728/MediaObjects/12864_2013_Article_7140_Fig2_HTML.jpg?as=webp"></source></picture> Differentially expressed genes per module. The bar plots indicate the ratio of F. graminearum responsive differentially expressed genes (DEG) per network module for 30 hours after inoculation (hai) (a) and 50 hai (b). To test whether the number of DEG genes was significantly higher than expected by chance we applied a one-sided Fisher's exact test. Stars indicate a significant enrichment at a Bonferroni adjusted p-value smaller than 0.05. Full size image<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-chevron-right"></use></svg> </figure> By using the module eigengenes [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 30" title="Langfelder P, Horvath S: Eigengene networks for studying the relationships between co-expression modules. BMC Syst Biol. 2007, 1: 54-10.1186/1752-0509-1-54." href="/articles/10.1186/1471-2164-14-728#ref-CR30" id="ref-link-section-d51289e1249">30, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 31" title="Langfelder P, Luo R, Oldham MC, Horvath S: Is my network module preserved and reproducible?. PLoS Comput Biol. 2011, 7: e1001057-10.1371/journal.pcbi.1001057." href="/articles/10.1186/1471-2164-14-728#ref-CR31" id="ref-link-section-d51289e1252">31] we found that modules B, G, and H were strongly linked to F. graminearum-inoculated samples (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM10">10). Of these modules two exhibited a general association to all genotypes at either both time points (module B) or only 50 hai (module G). Module H was strongly linked to the specific defense response of CM-82036 at 50 hai. Module A was also specific for CM-82036, but not for treatment or time point. A one-sided Fisher's exact test (significance threshold for Bonferroni adjusted p-values set to 0.05) was applied to test whether these modules showed a higher ratio of DEG than expected by chance. At 30 hai module B was strongly enriched for DEG for all five lines (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig2">2a) with CM-82036 exhibiting the highest relative amount of DEG (p = 7.0 e-48). This changed at 50 hai where all four NILs show a higher level of enrichment compared to CM-82036 (maximum p = 3.6 e-65; Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig2">2b). Also, 50 hai all lines exhibited a higher ratio of DEG for module G (maximum p = 1.7 e-02). Module H showed enrichment for CM-82036 at 30 hai (p = 1.9 e-02) as well as 50 hai (p = 2.7 e-07). We analyzed these data with GO and Interpro terms to obtain functional

annotations for the modules. Among others, DEG in the F. graminearum responsive module B encoded glutathione S-transferases (GST), UGTs, glucanases, protein kinases and WRKY transcription factors (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM11">11). For the CM-82036 related Module H and also for module G the few available GO terms did not provide sufficient meaningful annotations to predict specific molecular functions (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM11">11). Since module B is the by far largest module and highly enriched for F. graminearum responsive genes across all five lines, we further analyzed this module by splitting it into smaller submodules (deepsplit = 4; minimum module size = 10). The two largest submodules comprised 475 (B-sub1) and 397 genes (B-sub2), respectively. Submodule B-sub1 was significantly enriched for DEG in all genotypes at 50 hai but only few DEG (between 5% and 10% of module size) were identified at 30 hai (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM12">12). The relatively highest amount of DEG was found for the susceptible NIL4 and the moderately resistant NIL2. Only few GO terms were identified for this submodule (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM13">13). B-sub2 showed a strong enrichment for DEG at 30 hai for all genotypes (minimal p = 2.8 e-07). This enrichment was slightly more pronounced for CM-82036, NIL1 and NIL3. These three genotypes share the resistant allele of Qfhs.ifa-5A. Consequently, B-sub2 may be associated to the activity of Qfhs.ifa-5A. The majority of GO terms for DEG in this submodule were similar to the terms identified for the pool of DEG shared by genotypes harboring Qfhs.ifa-5A (see previous section). These corresponded to kinase activity, glutamate-gated ion channels and tRNA aminoacylation (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM13">13). <h3 class="c-article__sub-heading u-h3" id="Sec6">Defense-related central genes in the co-expression network</h3> A gene network allows quantifying the relative importance of single genes (nodes) by making use of local centrality measures [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 32" title="Freeman L: Centrality in social networks: conceptual clarification. Soc Networks. 1979, 1: 215-239." href="/articles/10.1186/1471-2164-14-728#ref-CR32" id="ref-link-section-d51289e1332">32–<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 34" title="Hage P, Harary F: Eccentricity and centrality in networks. Soc Networks. 1995, 17: 57-63. 10.1016/0378-8733(94)00248-9." href="/articles/10.1186/1471-2164-14-728#ref-CR34" id="ref-link-section-d51289e1335">34]. Multiple methods exist for assessing the centrality of nodes. Here we applied two methods for ranking the genes by their relative importance within the network: The degree centrality ranks nodes by the number of adjacent nodes within the network, which allows selecting so called hub genes. These hub genes often play important roles in the regulation of gene expression and may provide valuable insight into stress response or genome evolution [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 35" title="Jeong H, Mason SP, Barabasi AL, Oltvai ZN: Lethality and centrality in protein networks. Nature. 2001, 411: 41-42. 10.1038/35075138." href="/articles/10.1186/1471-2164-14-728#ref-CR35" id="ref-link-section-d51289e1338">35–<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 37" title="Ferreira RM, Rybarczyk-Filho JL, Dalmolin RJ, Castro MA, Moreira JC, Brunnet LG, de Almeida RM: Preferential duplication of intermodular hub genes: an evolutionary signature in eukaryotes genome networks. PloS one. 2013, 8: e56579-10.1371/journal.pone.0056579." href="/articles/10.1186/1471-2164-14-728#ref-CR37" id="ref-link-section-d51289e1341">37]. For our analysis we applied a weighted version of this measure as implemented in the igraph package [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 38" title="Csardi G, Nepusz T: The igraph software package for complex network research. InterJournal. 2006, Complex Systems: 1695-" href="/articles/10.1186/1471-2164-14-728#ref-CR38" id="ref-link-section-d51289e1344">38]. Additionally, we also made use of the eigenvector centrality [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 39" title="Bonacich P: Power and centrality: a family of measures. Am J Sociol. 1987, 92: 1170-1182. 10.1086/228631." href="/articles/10.1186/1471-2164-14-728#ref-CR39" id="ref-link-section-d51289e1348">39], which is related to eigenvectors of the largest eigenvalue of the adjacency matrix. To filter for the most important nodes from these

two measures we used the 90% percentile and deemed nodes with values higher than this threshold as being central within the network. We will further refer to degree centrality selected genes as DCG, and to Eigenvector centrality derived genes as ECG. In our network 218 central genes (ECG + DCG) were significantly regulated after F. graminearum inoculation and thus hold prominent roles in the wheat response to the pathogen. These central genes were also more likely differentially expressed in response to the pathogen than non-central genes in the network (Fisher's Exact Test, BH-adjusted p < 0.05). Most belong to module B and only few were identified in other modules. These genes were highly enriched for GO terms associated with signaling, ubiquitination, hypersensitive response and ATP binding. The latter two are GO terms commonly used to describe NBS-LRR resistance genes, which play crucial roles in pathogen reception and signal transduction. Additional terms corresponded to nucleotide binding, suggesting the involvement of transcription factors (including WRKY, for which we found also terms in module B). Interpro annotations further identified GSTs, CYPs, glucanases and UGTs (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM14">14). Both DCG and ECG are highly connected to other genes. Their expression behavior may have a strong impact on the global expression pattern within the network. When looking at genotype specific changes in expression of central genes, we found a group of 34 genes that were earlier differentially expressed for CM-82036 compared to the NILs. Three central genes, for which we could not retrieve annotations, were only transiently expressed. They were significantly changed for 30 hai but not 50 hai for CM-86036, while in the NILs these genes were differentially expressed only 50 hai. Yet, we detected no central genes that were only changed for CM-82036 but not for the NILs. On the other hand, 35 genes were differentially expressed exclusively for the NILs (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM15">15). When regarding genotypes differing in the presence of either QTL, we found five central genes earlier induced for Qfhs.ifa-5A: These encode four protein kinases and a CYP. Three of these are also present in the Qhfs.ifa-5A-associated submodule B-sub2. One of these genes XLOC_099598 encoding a protein kinase ranked third within the DCG, making it one of the highest connected central genes in our network. Similarly, we identified a UGT, an NBS-LRR and a putative disease resistance gene as earlier induced in lines containing Fhb1. <h3 class="c-article__sub-heading u-h3" id="Sec7">Gene family specific differential expression profiles</h3> The arms race between plants and pathogens has led to the rapid evolution of genes involved in the interaction with the pathogen and consequently to an increase in copy numbers to form large gene families. This allows plants to adapt to new challenges or to overcome detrimental effects of random mutagenesis by redundant gene function. The present study has among others identified glucanases, NBS-LRR proteins, WRKY transcription factors and UGTs as relevant factors in the F. graminearum/wheat interaction – each representing a certain stage in the host defense response (recognition, signal transduction, defense regulation and toxin inactivation). To further elucidate genotype and time point specific abundance of such transcripts we expanded our analysis by taking into account the entire gene families. We extracted Cufflinks genes encoding glucanases, NBS-LRR proteins, WRKYs and UGT using either domain specific motifs or homology information, clustered the acquired sequences using CLUSTALX N-J bootstrapping [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 40" title="Larkin MA, Blackshields G, Brown NP, Chenna R, McGettigan PA, McWilliam H, Valentin F, Wallace IM, Wilm A, Lopez R, Thompson JD, Gibson TJ, Higgins DG: Clustal w and clustal x version 2.0. Bioinformatics. 2007, 23: 2947-2948. 10.1093/bioinformatics/btm404." href="/articles/10.1186/1471-2164-14-728#ref-CR40" id="ref-link-section-d51289e1391">40] and added genotype-specific DEG information (Table <a data-track="click" data-track-label="link" data-track-action="table anchor" href="/articles/10.1186/1471-2164-14-728#Tab2">2). Using this approach we identified 568 putative wheat glucanase genes via mapping against barley genes that contained the Interpro domain IPR008985. Given the hexaploid nature of wheat, a reasonable high number compared to the 262 putative glucanases in barley [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 20" title="The International Barley Genome Sequencing Consortium: A physical, genetic and functional sequence assembly of the barley genome. Nature. 2012, 491: 711-716." href="/articles/10.1186/1471-2164-14-728#ref-CR20" id="ref-link-section-d51289e1397">20]. Similarly, we identified 246 NBS-LRR genes via mapping against 267 barley genes (http://www.vmatch.de), 116 WRKY transcription factors (74 in barley) via mapping against a conserved motif (WRKYGQK) and 222 putative UGTs (159 predicted functional genes in Brachypodium distachyon Beauv., [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-

test="citation-ref" aria-label="Reference 41" title="Schweiger W, Pasquet JC, Nussbaumer T, Kovalsky Paris MP, Wiesenberger G, Macadre C, Ametz C, Berthiller F, Lemmens M, Saindrenan P, Mewes HW, Mayer KF, Dufresne M, Adam G: Functional characterization of two clusters of Brachypodium distachyon UDP-glycosyltransferases encoding putative deoxynivalenol detoxification genes. Mol Plant-Microbe Interact. 2013, 26: 781-792. 10.1094/MPMI-08-12-0205-R." href="/articles/10.1186/1471-2164-14-728#ref-CR41" id="ref-link-section-d51289e1411">41]) by searching for the conserved signature motifs [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 42" title="Eulgem T, Rushton PJ, Robatzek S, Somssich IE: The WRKY superfamily of plant transcription factors. Trends Plant Sci. 2000, 5: 199-206. 10.1016/S1360-1385(00)01600-9." href="/articles/10.1186/1471-2164-14-728#ref-CR42" id="ref-link-section-d51289e1414">42, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 43" title="Vogt T, Jones P: Glycosyltransferases in plant natural product synthesis: characterization of a supergene family. Trends Plant Sci. 2000, 5: 1360-1385." href="/articles/10.1186/1471-2164-14-728#ref-CR43" id="ref-link-section-d51289e1417">43]. <figure><figcaption class="c-article-table__figcaption">Table 2
771 Differential expression of pathogen-induced gene families
772 </figcaption> Full size table<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-chevron-right"></use></svg> </figure> The DEG profiles for the NBS-LRR and glucanase genes showed dramatic differences between CM-82036 and the NILs at 30 hai: 36 of 44 differentially expressed NBS-LRR genes and 83 of 112 differentially expressed glucanases were found changed for CM-82036 and about half of those genes were only changed for this genotype and not for the NILs. In contrast only 7 to 11 of the NBS-LRR and 35 to 48 of the glucanases were differentially expressed for the NILs. 50 hai all genotypes showed an equally high number of upregulated NBS-LRR and glucanase genes (up to 35% of the total number of identified NBS-LRR and glucanase genes). The dominance in gene numbers and genotype specific genes for CM-82036 at 30 hai was not observed at 50 hai. Neither for glucanases (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM16">16), nor for NBS-LRR (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM17">17) we observed differential expression patterns that would suggest an Fhb1- or Qfhs.ifa-5A-dependent upregulation of genes. Members of the WRKY transcription factors play a decisive role in regulating response to abiotic and biotic stresses [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 42" title="Eulgem T, Rushton PJ, Robatzek S, Somssich IE: The WRKY superfamily of plant transcription factors. Trends Plant Sci. 2000, 5: 199-206. 10.1016/S1360-1385(00)01600-9." href="/articles/10.1186/1471-2164-14-728#ref-CR42" id="ref-link-section-d51289e2154">42]. While CM-82036 showed a stronger response at 30 hai (14 genes), we also found a relatively high number (10) of WRKY upregulated for the more the resistant NIL1 (containing Fhb1 and Qfhs-ifa.5A) compared to the moderately to susceptible NILs (NIL2-4), as depicted for 30 hai in Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig3">3a and for 50 hai in Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig3">3b). Potentially, the activity of both QTL leads to the (stacked) activation of multiple WRKY genes. In contrast to the NBS-LRR and glucanase gene families we found relatively less WRKY genes differentially expressed at 50 hai: No more than 20% of the 116 identified WRKY genes were differentially expressed for any genotype. <figure><figcaption>Figure 3</figcaption> <picture><source type="image/webp" srcset="//media.springernature.com/lw685/springer-

static/image/art%3A10.1186%2F1471-2164-14-728/MediaObjects/12864_2013_Article_7140_Fig3_HTML.jpg?as=webp"></source></picture> Regulation of WRKY genes at different time points. Dendrograms display differential expression of WRKY genes (a) 30 and (b) 50 hours after inoculation (hai) with F. graminearum spores. Genes that are significantly changed for the given genetic background (NIL1-NIL4, CM-82036) in response to F. graminearum are indicated in the respective color. Note that the clades within dendrogram do not necessarily reflect groups or families of related genes, but are only used for presentation purposes. Full size image<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-chevron-right"></use></svg> </figure> UGTs have been shown to encode the ability to inactivate the F. graminearum toxin DON by formation of DON-3-glucoside in Arabidopsis thaliana Heynh. (D3G, [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 44" title="Poppenberger B, Berthiller F, Lucyshyn D, Sieberer T, Schuhmacher R, Krska R, Kuchler K, Glossl J, Luschnig C, Adam G: Detoxification of the fusarium mycotoxin deoxynivalenol by a UDP-glucosyltransferase from Arabidopsis thaliana. J Biol Chem. 2003, 278: 47905-47914. 10.1074/jbc.M307552200." href="/articles/10.1186/1471-2164-14-728#ref-CR44" id="ref-link-section-d51289e2212">44]) and such genes also exist in monocotyledoneous species, where they are specifically upregulated in response to the toxin [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 41" title="Schweiger W, Pasquet JC, Nussbaumer T, Kovalsky Paris MP, Wiesenberger G, Macadre C, Ametz C, Berthiller F, Lemmens M, Saindrenan P, Mewes HW, Mayer KF, Dufresne M, Adam G: Functional characterization of two clusters of Brachypodium distachyon UDP-glycosyltransferases encoding putative deoxynivalenol detoxification genes. Mol Plant-Microbe Interact. 2013, 26: 781-792. 10.1094/MPMI-08-12-0205-R." href="/articles/10.1186/1471-2164-14-728#ref-CR41" id="ref-link-section-d51289e2215">41, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 45" title="Schweiger W, Boddu J, Shin S, Poppenberger B, Berthiller F, Lemmens M, Muehlbauer GJ, Adam G: Validation of a candidate deoxynivalenol-inactivating UDP-glucosyltransferase from barley by heterologous expression in yeast. Mol Plant-Microbe Interact. 2010, 23: 977-986. 10.1094/MPMI-23-7-0977." href="/articles/10.1186/1471-2164-14-728#ref-CR45" id="ref-link-section-d51289e2218">45]. Our analysis found relatively few UGTs responsive to F. graminearum compared to the total of 222 identified putative UGTs (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig4">4). We found no specific upregulation of UGTs in lines sharing Fhb1, the QTL associated with detoxification by glycoconjugation of the F. graminearum toxin DON ([<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 11" title="Lemmens M, Scholz U, Berthiller F, Dall'Asta C, Koutnik A, Schuhmacher R, Adam G, Buerstmayr H, Mesterhazy A, Krska R, Ruckenbauer P: The ability to detoxify the mycotoxin deoxynivalenol colocalizes with a major quantitative trait locus for fusarium head blight resistance in wheat. Mol Plant-Microbe Interact. 2005, 18: 1318-1324. 10.1094/MPMI-18-1318." href="/articles/10.1186/1471-2164-14-728#ref-CR11" id="ref-link-section-d51289e2234">11]). However, 50 hai, besides CM-82036 (27 differential expressed genes), NIL2, harboring Fhb1 only, exhibited the highest number of significantly changed UGTs (24). Also, while most of the DEG were found in more than just one NIL, 6 UGTs are only differentially expressed for NIL2. Recently, we have characterized a monocotyledonous UGT gene family, which encodes isozymes capable of inactivating the toxin [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 41" title="Schweiger W, Pasquet JC, Nussbaumer T, Kovalsky Paris MP, Wiesenberger G, Macadre C, Ametz C, Berthiller F, Lemmens M, Saindrenan P, Mewes HW, Mayer KF, Dufresne M, Adam G: Functional characterization of two clusters of Brachypodium distachyon UDP-glycosyltransferases encoding putative deoxynivalenol detoxification genes. Mol Plant-Microbe Interact. 2013, 26: 781-792. 10.1094/MPMI-08-12-0205-R." href="/articles/10.1186/1471-2164-14-728#ref-CR41" id="ref-link-section-

d51289e2241">41]. We have identified nine putative orthologs to this gene family in our data (highlighted in Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig4">4a and <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig4">4b) of which 2 were again specifically changed only for NIL2 at 50 hai (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig4">4b), while the others were either not differentially expressed at all (3) or upregulated in more than one genotype without exhibiting any QTL dependent patterns (4). <figure><figcaption>Figure 4</figcaption> <picture><source type="image/webp" srcset="//media.springernature.com/lw685/springer-static/image/art%3A10.1186%2F1471-2164-14-728/MediaObjects/12864_2013_Article_7140_Fig4_HTML.jpg?as=webp"></source></picture> Regulation of UGT genes at different time points. Dendrograms display differential expression of UGT genes (a) 30 and (b) 50 hours after inoculation (hai) with F. graminearum spores. Genes that are significantly changed for the given genetic background (NIL1-NIL4, CM-82036) in response to F. graminearum are indicated in the respective colour. UGT genes homologous to the previously identified DON-detoxification UGTs in B. distachyon are highlighted. Note that the clades within dendrogram do not necessarily reflect groups or families of related genes, but are only used for presentation purposes. Full size image<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-chevron-right"></use></svg> </figure> </section><section aria-labelledby="Sec8"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Sec8">Discussion</h2>
The defense response of wheat to one of its most devastating pathogens F. graminearum has been investigated in multiple transcriptome profiling studies, which compared differentially resistant genotypes [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 46" title="Jia H, Cho S, Muehlbauer GJ: Transcriptome analysis of a wheat near-isogenic line pair carrying fusarium head blight–resistant and –susceptible alleles. Mol Plant-Microbe Interact. 2009, 22: 1366-1378. 10.1094/MPMI-22-11-1366." href="/articles/10.1186/1471-2164-14-728#ref-CR46" id="ref-link-section-d51289e2300">46–<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 48" title="Gottwald S, Samans B, Luck S, Friedt W: Jasmonate and ethylene dependent defence gene expression and suppression of fungal virulence factors: two essential mechanisms of fusarium head blight resistance in wheat?. BMC genomics. 2012, 13: 369-10.1186/1471-2164-13-369." href="/articles/10.1186/1471-2164-14-728#ref-CR48" id="ref-link-section-d51289e2303">48] or reported on the specific response to DON [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 49" title="Walter S, Brennan J, Trognitz F, Trognitz B, Leonard G, Egan D, Doohan F: Components of the gene network associated with genotype-dependent response of wheat to the fusarium mycotoxin deoxynivalenol. Funct Integr Genomics. 2008, 8: 421-427. 10.1007/s10142-008-0089-4." href="/articles/10.1186/1471-2164-14-728#ref-CR49" id="ref-link-section-d51289e2306">49–<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 51" title="Ansari KI, Walter S, Brennan JM, Lemmens M, Kessans S, McGahern A, Egan D, Doohan FM: Retrotransposon and gene activation in wheat in response to mycotoxigenic and non-mycotoxigenic-associated fusarium stress. Theor Appl Genet. 2007, 114: 927-937. 10.1007/s00122-006-0490-0." href="/articles/10.1186/1471-2164-14-728#ref-CR51" id="ref-link-section-d51289e2309">51]. The general understanding of the wheat/F. graminearum interaction has been further expanded by proteomic and

metabolomic studies [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 12" title="Gunnaiah R, Kushalappa AC, Duggavathi R, Fox S, Somers DJ: Integrated metabolo-proteomic approach to decipher the mechanisms by which wheat QTL (Fhb1) contributes to resistance against Fusarium graminearum. PloS one. 2012, 7: e40695-10.1371/journal.pone.0040695." href="/articles/10.1186/1471-2164-14-728#ref-CR12" id="ref-link-section-d51289e2316">12, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 52" title="Ding L, Xu H, Yi H, Yang L, Kong Z, Zhand L, Xue S, Jia H: Resistance to hemi-biotrophic F. graminearum infection is associated with coordinated and ordered expression of diverse defense signaling pathways. PloS one. 2011, 6: e19008-10.1371/journal.pone.0019008." href="/articles/10.1186/1471-2164-14-728#ref-CR52" id="ref-link-section-d51289e2319">52]. Statistics on large-scale data often rely on the detection of isolated significantly changed genes. These genes represent only a fraction of the entire defense response and potentially might not include the causative gene for mounting the resistant reaction. Here we present a co-expressed gene network, which enabled us to detect gene modules that are active in the susceptible and/or resistant genotypes. A network-driven approach has the advantage of describing coordinated gene expression changes in a holistic manner [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 53" title="Emmert-Streib F, Dehmer M: Networks for systems biology: conceptual connection of data and function. IET Syst Biol. 2011, 5: 185-207. 10.1049/iet-syb.2010.0025." href="/articles/10.1186/1471-2164-14-728#ref-CR53" id="ref-link-section-d51289e2322">53]. The interaction information can then be analyzed using mathematical approaches that can select features of interest for the subsequent analyses, e.g. [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 54" title="Todeschini R, Consonni V: Handbook of Molecular Descriptors. 2008, Weilheim: WILEY-VCH" href="/articles/10.1186/1471-2164-14-728#ref-CR54" id="ref-link-section-d51289e2325">54, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 55" title="Mueller LA, Kugler KG, Dander A, Graber A, Dehmer M: QuACN: an R package for analyzing complex biological networks quantitatively. Bioinformatics. 2011, 27: 140-141. 10.1093/bioinformatics/btq606." href="/articles/10.1186/1471-2164-14-728#ref-CR55" id="ref-link-section-d51289e2328">55]. Integration of DEG information into the gene co-expression network allowed for observing genotype specific dynamics in the response. In the work at hand we analyzed the effect of two major QTL by analyzing gene expression profiles of NILs segregating for either QTL. The identified modules comprise groups of genes that act in concerted manner in reaction to the pathogen – and in part are also specific for genotype or the QTL. It needs however to be noted that these effects may also be influenced by the activity of closely linked, yet QTL independent genes, that have been introgressed with the QTL during the generation of the near-isogenic material. To understand the functional background of these modules it will be necessary to combine information about the genes in these modules and their interactions with additional data, which will be part of future studies. The publication of the bread wheat genome will contribute to this challenge by allowing to further split the network into subgenome-specific partitions. The time points we chose to collect samples after inoculation with F. graminearum reflect crucial stages of the initial biotrophic growth phase of F. graminearum (30 hai) and in the onset of necrotrophic growth (50 hai): Germination and hyphae development occurs within 24 hai and the formation of infection hyphae has been observed at 36 hai [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 56" title="Seong KY, Zhao X, Xu JR, Guldener U, Kistler HC: Conidial germination in the filamentous fungus Fusarium graminearum. Fung Genet Biol. 2008, 45: 389-399. 10.1016/j.fgb.2007.09.002." href="/articles/10.1186/1471-2164-14-728#ref-CR56" id="ref-link-section-d51289e2340">56]. The colonization of cells and spread into rachis and adjacent spikelet is reported to occur at about 48 hai [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 57" title="Pritsch C, Muehlbauer GJ, Bushnell WR, Somers DA, Vance CP: Fungal development and induction of defense response genes during early infection of wheat spikes by Fusarium graminearum. Mol Plant-Microbe Interact. 2000, 13: 159-169. 10.1094/MPMI.2000.13.2.159." href="/articles/10.1186/1471-2164-14-728#ref-CR57" id="ref-link-section-d51289e2343">57]. Significant levels of DON were only found after this time point [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol

Plant Pathol. 2013, 14: 772-785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e2346">14, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 46" title="Jia H, Cho S, Muehlbauer GJ: Transcriptome analysis of a wheat near-isogenic line pair carrying fusarium head blight–resistant and –susceptible alleles. Mol Plant-Microbe Interact. 2009, 22: 1366-1378. 10.1094/MPMI-22-11-1366." href="/articles/10.1186/1471-2164-14-728#ref-CR46" id="ref-link-section-d51289e2350">46]. We observed two distinct defense-related modules in the gene co-expression network, which showed a time point dependent enrichment with DEG. Module B, comprising well over 1,000 genes in our network, was significantly enriched for genes upregulated in presence of the pathogen already at 30 hai and more so at 50 hai. In contrast module G was significantly enriched for DEG only at 50 hai. Potentially, module G could reflect reaction to the transformation of the fungus into the necrotrophic stage and possibly to DON, which is not likely to be present earlier. Module G was higher enriched for the more susceptible genotypes NIL2 (Fhb1) and NIL4 (no QTL) but also for CM-82036. NIL2 and NIL4 lack the resistance against initial infection conferred by Qfhs.ifa-5A and consequently a higher infection rate could have elicited a stronger response in these genotypes. The enrichment for CM-82036 may correspond to a general faster induction of defense mechanisms. <h3 class="c-article__sub-heading u-h3" id="Sec9">Activation of glycolysis and amino acid biosynthesis in response to F. graminearum</h3> Our analysis finds genes involved in the pentose phosphate pathway and citric acid cycle upreguated in response to the pathogen in all genotypes. Additional terms for the pentose phosphate pathway and also for the glutathione-mediated detoxification of the toxic respiration biproduct methylglyoxal (glyoxylase I, [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 58" title="Dixon DP, Cummins I, Cole DJ, Edwards R: Glutathione-mediated detoxification systems in plants. Curr Opin Plant Biol. 1998, 1: 258-266. 10.1016/S1369-5266(98)80114-3." href="/articles/10.1186/1471-2164-14-728#ref-CR58" id="ref-link-section-d51289e2369">58]) have been found for NIL3. These findings demonstrate the elevated demand of carbohydrates and energy equivalents during the resistance response and also the probable breakdown of photosynthesis, which is required to replenish energy equivalents from carbohydrates (reviewed in [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 28" title="Seifi HS, Van Bockhaven J, Angenon G, Hofte M: Glutamate metabolism in plant disease and defense: friend or foe?. Mol Plant-Microbe Interact. 2013, 26: 475-485. 10.1094/MPMI-07-12-0176-CR." href="/articles/10.1186/1471-2164-14-728#ref-CR28" id="ref-link-section-d51289e2372">28]). The glycolysis-generated NADPH could also be used to fuel the production of reactive oxygen species. However, we do not find terms for the central enzyme in production of reactive oxygen species (ROS), NADPH oxidase in our analysis. Acquisition of the required hexoses heavily relies on the activity of cell wall invertases, which have also not been detected in our analysis. Transient silencing of a tobacco invertase, severely reduces the expression of defense-related genes [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 59" title="Essmann J, Schmitz-Thom I, Schon H, Sonnewald S, Weis E, Scharte J: RNA interference-mediated repression of cell wall invertase impairs defense in source leaves of tobacco. Plant physiol. 2008, 147: 1288-1299. 10.1104/pp.108.121418." href="/articles/10.1186/1471-2164-14-728#ref-CR59" id="ref-link-section-d51289e2375">59]. However, invertase activity might not be sufficient to meet the increased requirements. The citric acid cycle can be replenished via the GABA-shunt, which utilizes glutamate as substrate [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 29" title="Langfelder P, Horvath S: WGCNA: an R package for weighted correlation network analysis. BMC bioinformatics. 2008, 9: 559-10.1186/1471-2105-9-559." href="/articles/10.1186/1471-2164-14-728#ref-CR29" id="ref-link-section-d51289e2378">29]. We find GO terms for glutamate synthases and glutamine metabolic processes abundant already 30 hai, which could be upregulated to support the GABA-shunt. An alternative explanation suggests an indirect role in the production of secondary metabolites: Glutamine synthase have been shown upregulated in concert with phenylalanine ammonia lyases (PAL), which catalyse the transformation of phenylalanine to trans-cinnamate and represent the first dedicated step in the biosynthesis of phenylpropanoids and lignin. Ammonium is a side product of this process and may be reutilized by glutamine synthases also in order to prevent the accumulation to toxic levels. <h3 class="c-article__sub-heading u-h3" id="Sec10">The resistant CM-82036 exerts its successful defense by reacting earlier and with a specific subnetwork</h3> The unique response of CM-82036 was already reflected in the high number of DEG at 30 hai in comparison to the four NILs. Also for CM-82036 a much higher number of glucanases, NBS-LRR and WRKY genes were activated earlier. The faster response in

comparison to susceptible genotypes has been previously observed [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 57" title="Pritsch C, Muehlbauer GJ, Bushnell WR, Somers DA, Vance CP: Fungal development and induction of defense response genes during early infection of wheat spikes by Fusarium graminearum. Mol Plant-Microbe Interact. 2000, 13: 159-169. 10.1094/MPMI.2000.13.2.159." href="/articles/10.1186/1471-2164-14-728#ref-CR57" id="ref-link-section-d51289e2389">57]. Not only transcript levels of putative resistance genes but also faster induction of such genes seem to be a decisive factor in mounting a successful defense response [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 48" title="Gottwald S, Samans B, Luck S, Friedt W: Jasmonate and ethylene dependent defence gene expression and suppression of fungal virulence factors: two essential mechanisms of fusarium head blight resistance in wheat?. BMC genomics. 2012, 13: 369-10.1186/1471-2164-13-369." href="/articles/10.1186/1471-2164-14-728#ref-CR48" id="ref-link-section-d51289e2392">48, <a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 52" title="Ding L, Xu H, Yi H, Yang L, Kong Z, Zhand L, Xue S, Jia H: Resistance to hemi-biotrophic F. graminearum infection is associated with coordinated and ordered expression of diverse defense signaling pathways. PloS one. 2011, 6: e19008-10.1371/journal.pone.0019008." href="/articles/10.1186/1471-2164-14-728#ref-CR52" id="ref-link-section-d51289e2395">52]. What distinguished the response of CM-82036 was also a unique response module (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig2">2 Module H), which was not observed for any of the other lines. Besides genes involved in signaling and control of gene expression GO annotations of this module highlight terms for terpenoid and trehalose biosynthesis at 30 hai. The role of the disaccharide trehalose in plant defense has been recently reviewed [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 60" title="Fernandez O, Bethencourt L, Quero A, Sangwan RS, Clement C: Trehalose and plant stress responses: friend or foe?. Trends Plant Sci. 2010, 15: 409-417. 10.1016/j.tplants.2010.04.004." href="/articles/10.1186/1471-2164-14-728#ref-CR60" id="ref-link-section-d51289e2401">60]. Trehalose has been reported as a ROS quencher in wheat [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 61" title="Luo Y, Li W-M, Wang W: Trehalose: protector of antioxidant enzymes or reactive oxygen species scavenger under heat stress?. Environ Exper Bot. 2008, 63: 378-384. 10.1016/j.envexpbot.2007.11.016." href="/articles/10.1186/1471-2164-14-728#ref-CR61" id="ref-link-section-d51289e2405">61] and induces the expression of a WRKY6 gene and a glucanase gene in A. thaliana[<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 28" title="Seifi HS, Van Bockhaven J, Angenon G, Hofte M: Glutamate metabolism in plant disease and defense: friend or foe?. Mol Plant-Microbe Interact. 2013, 26: 475-485. 10.1094/MPMI-07-12-0176-CR." href="/articles/10.1186/1471-2164-14-728#ref-CR28" id="ref-link-section-d51289e2411">28]. Treatment with trehalose confers partial protection against Blumeria graminis Speer to wheat [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 62" title="Renard-Merlier D, Randoux B, Nowak E, Farcy F, Durand R, Reignault P: Iodus 40, salicylic acid, heptanoyl salicylic acid and trehalose exhibit different efficacies and defence targets during a wheat/powdery mildew interaction. Phytochem. 2007, 68: 1156-1164. 10.1016/j.phytochem.2007.02.011." href="/articles/10.1186/1471-2164-14-728#ref-CR62" id="ref-link-section-d51289e2417">62]. The present study also found a considerable higher number of glucanase genes significantly changed for the earlier time point compared to the other investigated genotypes, which could relate to trehalose activity. However, it remains unclear as how the sugar exerts these functions. <h3 class="c-article__sub-heading u-h3" id="Sec11">A diacylglycerol kinase and early induction of JA and ET biosynthesis are associated with lines harboring Fhb1</h3> We have observed effects of Fhb1 in different genetic backgrounds by identifying F. graminearum responsive transcripts that are changed only for lines harboring the resistant Fhb1 allele. Among the few shared transcripts we found terms for G protein coupled signaling and diacylglycerol kinase activity (describing the same gene, 30 and 50 hai). Loss of G protein dependent phosphatidic acid signaling leads to reduced accumulation of defense-associated transcripts: Plant G proteins act in reception and translation of extracellular cues into intracellular second messengers. In rice the expression of the G protein α subunit RGA1 is R-gene dependent and rga1 mutants show a delayed production of ROS in response to Magnaporthe grisea Barr elicitors [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 63" title="Suharsono U,

Fujisawa Y, Kawasaki T, Iwasaki Y, Satoh H, Shimamoto K: The heterotrimeric G protein alpha subunit acts upstream of the small GTPase Rac in disease resistance of rice. Proc Natl Acad Sci U S A. 2002, 99: 13307-13312. 10.1073/pnas.192244099." href="/articles/10.1186/1471-2164-14-728#ref-CR63" id="ref-link-section-d51289e2451">63]. The same authors could later show that a mitogen-activated protein kinase is the downstream target of RGA1. Silencing this kinase leads to reduced levels of PR proteins and PAL [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 64" title="Lieberherr D, Thao NP, Nakashima A, Umemura K, Kawasaki T, Shimamoto K: A sphingolipid elicitor-inducible mitogen-activated protein kinase is regulated by the small GTPase OsRac1 and heterotrimeric G-protein in rice 1[w]. Plant Physiol. 2005, 138: 1644-1652. 10.1104/pp.104.057414." href="/articles/10.1186/1471-2164-14-728#ref-CR64" id="ref-link-section-d51289e2454">64]. A role for phosphatidic acid signaling in F. graminearum resistance was previously suggested by Ding and associates [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 52" title="Ding L, Xu H, Yi H, Yang L, Kong Z, Zhand L, Xue S, Jia H: Resistance to hemi-biotrophic F. graminearum infection is associated with coordinated and ordered expression of diverse defense signaling pathways. PloS one. 2011, 6: e19008-10.1371/journal.pone.0019008." href="/articles/10.1186/1471-2164-14-728#ref-CR52" id="ref-link-section-d51289e2463">52]. In this proteomic/transcriptomic study the authors find among other transcripts also diacylglycerol kinase and phospholipase D less abundant in a F. graminearum-susceptible mutant of the Fhb1-harboring resistant line Wangshuibai. Also in A. thaliana mutants of the G protein β subunit ABG1 were shown more susceptible to a variety of fungal pathogens, including Fusarium oxysporum Schltdl. [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 65" title="Trusov Y, Rookes JE, Chakravorty D, Armour D, Schenk PM, Botella JR: Heterotrimeric G proteins facilitate arabidopsis resistance to necrotrophic pathogens and are involved in jasmonate signaling. Plant Physiol. 2006, 140: 210-220." href="/articles/10.1186/1471-2164-14-728#ref-CR65" id="ref-link-section-d51289e2479">65]. The expression of Fhb1-related genes could be coupled to disease development/presence of DON and hence to the overall resistance conferred by the respective genotype, which may delay disease development to a certain extent. The lines containing Fbh1 exhibit broad differences in FHB resistance: The highly resistant CM-82036 develops disease symptoms exclusively on the infected spikelets, while NIL1 (both QTL) and NIL2 (only Fhb1) exhibit just an intermediate level of resistance [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol Plant Pathol. 2013, 14: 772-785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e2494">14]. Consequently, Fhb1-associated transcripts are not necessarily significantly changed for all these lines at a given time point. To reduce complexity, we have also investigated DEG for NIL2 only, which harbors Fhb1 in a susceptible background. DEG encoded for proteins involved in the biosynthesis of biotic stress response hormones JA and ET already at 30 hai. Both have been implicated with resistance mediated by the QTL donor line Sumai-3 [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 66" title="Li G, Yen Y: Jasmonate and ethylene signaling pathway may mediate fusarium head blight resistance in wheat. Crop Sci. 2008, 48: 1888-1896. 10.2135/cropsci2008.02.0097." href="/articles/10.1186/1471-2164-14-728#ref-CR66" id="ref-link-section-d51289e2504">66]. Recent work using Virus-induced gene silencing in wheat showed that plants impaired in the production of ET are more susceptible to the disease [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 67" title="Gillespie ME, Brandt AS, Scofield SR: Ethylene-signaling is essential for basal resistance to Fusarium head blight in wheat. Proceedings of the National Fusarium Head Blight Forum: 4-6 December 2012; Orlando, FL. Edited by: Canty S. 2012, East Lansing, MI/Lexington, KY: US Wheat & Barley Scab Initiative, 135-" href="/articles/10.1186/1471-2164-14-728#ref-CR67" id="ref-link-section-d51289e2507">67]. JA has also received some attention in respect of Fhb1 recently: The QTL was associated with a higher abundance of JA in a proteomic study using a NIL pair differing in Fhb1[<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 50" title="Lulin M, Yi S, Aizhong C, Zengjun Q, Liping X, Peidu C, Dajun L, Xiu EW: Molecular cloning and characterization of an up-regulated UDP-

glucosyltransferase gene induced by DON from Triticum aestivum L. cv. Wangshuibai. Mol Biol Rep. 2010, 37: 785–795. 10.1007/s11033-009-9606-3." href="/articles/10.1186/1471-2164-14-728#ref-CR50" id="ref-link-section-d51289e2516">50]. In the first transcriptome sequencing study investigating an Fhb1-deletion line of Wangshuibai, the authors find no difference in the abundance of transcripts corresponding to JA biosynthesis genes, but hypothesize that JA signaling in the deletion line is impaired, since downstream targets of JA are induced in the wildtype but not in the deletion line [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 61" title="Luo Y, Li W-M, Wang W: Trehalose: protector of antioxidant enzymes or reactive oxygen species scavenger under heat stress?. Environ Exper Bot. 2008, 63: 378–384. 10.1016/j.envexpbot.2007.11.016." href="/articles/10.1186/1471-2164-14-728#ref-CR61" id="ref-link-section-d51289e2523">61]. These findings may be related to the Fhb1-associated G protein coupled kinase, which could be involved in transmitting JA signals. Fhb1 confers resistance against spreading of the disease [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 9" title="Buerstmayr H, Lemmens M, Hartl L, Doldi L, Steiner B, Stierschneider M, Ruckenbauer P: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. I. Resistance to fungal spread (Type II resistance). Theor Appl Genet. 2002, 104: 84–91. 10.1007/s001220200009." href="/articles/10.1186/1471-2164-14-728#ref-CR9" id="ref-link-section-d51289e2534">9]. The QTL also co-localizes with resistance against DON – a virulence factor for F. graminearum[<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 11" title="Lemmens M, Scholz U, Berthiller F, Dall’Asta C, Koutnik A, Schuhmacher R, Adam G, Buerstmayr H, Mesterhazy A, Krska R, Ruckenbauer P: The ability to detoxify the mycotoxin deoxynivalenol colocalizes with a major quantitative trait locus for fusarium head blight resistance in wheat. Mol Plant-Microbe Interact. 2005, 18: 1318–1324. 10.1094/MPMI-18-1318." href="/articles/10.1186/1471-2164-14-728#ref-CR11" id="ref-link-section-d51289e2540">11] and it is very likely that both QTL relate to the same causal gene. Consequently, the QTL may exert its function only in the necrotrophic growth phase of the fungus. The resistant response in NIL2 appears delayed when observing dynamics of gene expression for four closer characterized gene families (Figures <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig3">3 and <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig4">4, Additional files <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM16">16 and <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM17">17). While CM-82036 exhibits the highest number of DEG at 30 hai for glucanase, NBS-LRR, WRKY and UGT genes, NIL2 and NIL4 show fewer DEG than the other lines at this time point. At 50 hai many more genes are upregulated for all genotypes (Table <a data-track="click" data-track-label="link" data-track-action="table anchor" href="/articles/10.1186/1471-2164-14-728#Tab2">2). By then, NIL2 has caught up and exhibits a similar strong response as CM-82036, while NIL4 still contains among the lowest number of DEG. The stronger response for NIL2 at 50 hai, could suggest the requirement of additional environmental cues such as penetration of host tissue/DON accumulation, which may not be present at 30 hai. Especially the UGT gene family is interesting in respect of Fhb1: Lines harboring the QTL contain a higher ratio of the UGT-mediated DON detoxification product DON-3-glucoside [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 11" title="Lemmens M, Scholz U, Berthiller F, Dall’Asta C, Koutnik A, Schuhmacher R, Adam G, Buerstmayr H, Mesterhazy A, Krska R, Ruckenbauer P: The ability to detoxify the mycotoxin deoxynivalenol colocalizes with a major quantitative trait locus for fusarium head blight resistance in wheat. Mol Plant-Microbe Interact. 2005, 18: 1318–1324. 10.1094/MPMI-18-1318." href="/articles/10.1186/1471-2164-14-728#ref-CR11" id="ref-link-section-d51289e2562">11]. Wheat UGTs orthologous to a recently described gene cluster of B. distachyon[<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 41" title="Schweiger W, Pasquet JC, Nussbaumer T, Kovalsky Paris MP, Wiesenberger G, Macadre C, Ametz C, Berthiller F, Lemmens M, Saindrenan P, Mewes HW, Mayer KF, Dufresne M, Adam G: Functional characterization of two clusters of Brachypodium distachyon UDP-glycosyltransferases encoding putative deoxynivalenol detoxification genes. Mol Plant-Microbe Interact. 2013, 26: 781–792. 10.1094/MPMI-08-12-0205-R." href="/articles/10.1186/1471-2164-14-728#ref-CR41" id="ref-link-section-d51289e2569">41] harboring DON-detoxification UGTs potentially share this ability. Our analysis identified 9 close homologs, which are likely candidates for future

functional analysis. 2 and 7 of these homologs are expressed 30 and 50 hai, respectively, which is in line with the observation that these UGTs are not induced by F. graminearum but specifically for the toxin [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 41" title="Schweiger W, Pasquet JC, Nussbaumer T, Kovalsky Paris MP, Wiesenberger G, Macadre C, Ametz C, Berthiller F, Lemmens M, Saindrenan P, Mewes HW, Mayer KF, Dufresne M, Adam G: Functional characterization of two clusters of Brachypodium distachyon UDP-glycosyltransferases encoding putative deoxynivalenol detoxification genes. Mol Plant-Microbe Interact. 2013, 26: 781-792. 10.1094/MPMI-08-12-0205-R." href="/articles/10.1186/1471-2164-14-728#ref-CR41" id="ref-link-section-d51289e2575">41]. However, only few genes are specifically induced in lines with Fhb1 or NIL2 only. <h3 class="c-article__sub-heading u-h3" id="Sec12">Lines harboring Qfhs.ifa-5Aexhibited higher activity in defense module B-sub2 and were associated with calcium signaling and riboflavin biosynthesis</h3> In contrast to Fhb1, Qfhs.ifa-5A confers type I resistance against initial infection of F. graminearum[<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 9" title="Buerstmayr H, Lemmens M, Hartl L, Doldi L, Steiner B, Stierschneider M, Ruckenbauer P: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. I. Resistance to fungal spread (Type II resistance). Theor Appl Genet. 2002, 104: 84-91. 10.1007/s001220200009." href="/articles/10.1186/1471-2164-14-728#ref-CR9" id="ref-link-section-d51289e2602">9]. Although the infection method used in this study favors the phenotypic assessment of type II resistance, the resistance mediated by Qfhs.ifa-5A can be assessed using this technique, and consequently also the QTL-specific transcriptional response may be captured. In this study we found more genes in the defense-associated network module B-sub2 differentially expressed for lines harboring Qfhs.ifa-5A at 30 hai (CM-82036, NIL1, NIL3) than for lines without the QTL. While this may not represent a QTL-specific gene subnetwork, we suggest that these genes were faster or stronger differentially expressed for these lines due to the activity of the Qfhs.ifa-5A. We identified a group of central genes encoding protein kinases and a CYP gene within this module, which were earlier induced for Qfhs.ifa-5A lines. These all are likely candidates for future functional analysis. Submodule B-sub2 comprised 397 genes and included kinases activity, glutamate-gated ion channels and genes involved in tRNA processing (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM13">13). Elevated tRNA abundance has been previously linked to the response to DON in barley [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 68" title="Gardiner S, Boddu J, Berthiller F, Hametner C, Stupar R, Adam G, Muehlbauer G: Transcriptome analysis of the barley-deoxynivalenol interaction: evidence for a role of glutathione in deoxynivalenol detoxification. Mol Plant-Microbe Interact. 2010, 23: 962-976. 10.1094/MPMI-23-7-0962." href="/articles/10.1186/1471-2164-14-728#ref-CR68" id="ref-link-section-d51289e2621">68] and other abiotic stresses [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 69" title="Wu XR, Kenzior A, Willmot D, Scanlon S, Chen Z, Topin A, He SH, Acevedo A, Folk WR: Altered expression of plant lysyl tRNA synthetase promotes tRNA misacylation and translational recoding of lysine. Plant J. 2007, 50: 627-636. 10.1111/j.1365-313X.2007.03076.x." href="/articles/10.1186/1471-2164-14-728#ref-CR69" id="ref-link-section-d51289e2624">69]. Higher translational activity could be a secondary effect to the toxin and not an active resistance response. Since, tRNA related terms are only found in the core set of DEG shared by all genotypes (Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig1">1), we conclude that these most likely are not related to the resistance conferred by Qfhs.ifa-5A. In contrast, the glutamate-gated ion channel identified in the submodule was also changed only for lines sharing the QTL in the DEG analysis at 30 hai. Endogenous or environmental factors trigger changes in apoplasmatic glutamate concentration, which leads to the activation of these channels and subsequently to an intracellular increase of Ca^{2+} [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 70" title="Dennison KL, Spalding EP: Glutamate-gated calcium fluxes in arabidopsis. Plant Physiol. 2000, 124: 1511-1514. 10.1104/pp.124.4.1511." href="/articles/10.1186/1471-2164-14-728#ref-CR70" id="ref-link-section-d51289e2636">70]. Ca^{2+} influx is associated with early defense signalling [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 71" title="Lecourieux D, Mazars C, Pauly N, Ranjeva R, Pugin A: Analysis and effects of cytosolic free calcium increases in response to elicitors in Nicotiana plumbaginifolia cells. Plant Cell. 2002, 14: 2627-2641. 10.1105/tpc.005579."

href="/articles/10.1186/1471-2164-14-728#ref-CR71" id="ref-link-section-d51289e2641">71]. Overexpression of ionotrophic glutamate receptors in A. thaliana leads to an increase in Ca²⁺ influx and consequently to a delayed infection with Botrytis cinerea Pers. [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 72" title="Kang S, Kim HB, Lee H, Choi JY, Heu S, Oh CJ, Kwon SI, An CS: Overexpression in arabidopsis of a plasma membrane-targeting glutamate receptor from small radish increases glutamate-mediated Ca2+ influx and delays fungal infection. Mol Cells. 2006, 21: 418-427." href="/articles/10.1186/1471-2164-14-728#ref-CR72" id="ref-link-section-d51289e2653">72]. Downstream targets of Ca²⁺ signaling such as ATPases or calmodulin are frequently reported as induced by F. graminearum (e.g. [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 52" title="Ding L, Xu H, Yi H, Yang L, Kong Z, Zhand L, Xue S, Jia H: Resistance to hemi-biotrophic F. graminearum infection is associated with coordinated and ordered expression of diverse defense signaling pathways. PloS one. 2011, 6: e19008-10.1371/journal.pone.0019008." href="/articles/10.1186/1471-2164-14-728#ref-CR52" id="ref-link-section-d51289e2662">52]). Genotypes harboring Qfhs.ifa-5A also share GO terms relating to the biosynthesis and the metabolism of riboflavin (30 hai). Riboflavin has been reported to induce resistance to fungal and other pathogens [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 73" title="Dong H, Beer SV: Riboflavin induces disease resistance in plants by activating a novel signal transduction pathway. Phytopathol. 2000, 90 (8): 801-811. 10.1094/PHYTO.2000.90.8.801." href="/articles/10.1186/1471-2164-14-728#ref-CR73" id="ref-link-section-d51289e2668">73], potentially by recruiting NPR1, the essential regulator of systemic acquired resistance, independently from the defense-signaling hormone salicylic acid, which is strongly associated with NPR1 [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 74" title="Zhang S, Yang X, Sun M, Sun F, Deng S, Dong H: Riboflavin-induced priming for pathogen defense in Arabidopsis thaliana. J Integr Plant Biol. 2009, 51: 167-174. 10.1111/j.1744-7909.2008.00763.x." href="/articles/10.1186/1471-2164-14-728#ref-CR74" id="ref-link-section-d51289e2671">74]. Riboflavin is also implicated in the activation of ethylene biosynthesis [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 73" title="Dong H, Beer SV: Riboflavin induces disease resistance in plants by activating a novel signal transduction pathway. Phytopathol. 2000, 90 (8): 801-811. 10.1094/PHYTO.2000.90.8.801." href="/articles/10.1186/1471-2164-14-728#ref-CR73" id="ref-link-section-d51289e2674">73] and we also find genes related to ethylene biosynthesis in the section shared by lines harboring Qfhs.ifa-5A (Additional file <a data-track="click" data-track-label="link" data-track-action="supplementary material anchor" href="/articles/10.1186/1471-2164-14-728#MOESM6">6, 30 hai). Taken together this study provides insights into resistance response of differentially resistant wheat genotypes to F. graminearum. By combining a gene co-expression network approach with differential gene expression analysis we were able to make observation of genes and pathways associated with two prominent resistance QTL, Fhb1 and Qfhs.ifa-5A. Central genes within the network may be valid candidate genes for functional testing. </section><section aria-labelledby="Sec13"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Sec13">Conclusions</h2> This RNA-seq study provides insights into the QTL-dependent defense response of bread wheat against F. graminearum. We find G-protein coupled receptor kinases and biosynthesis genes for jasmonate and ethylene earlier induced for NILs harboring Fhb1 and genes involved in the biosynthesis and metabolism of riboflavin were found more abundant after infection in lines harboring Qfhs.ifa-5A. By combining a gene co-expression network approach with differential gene expression analysis we identified genes and pathways associated with the investigated NILs and the resistant parent CM-82036. Central genes within the network may be promising candidate genes for functional testing. Revisiting these and other data after the complete wheat genes are available will provide even higher resolved insights into the defense response dynamics within the gene co-expression network. </section><section aria-labelledby="Sec14"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Sec14">Methods</h2> <h3 class="c-article__sub-heading u-h3" id="Sec15">Plant material and inoculation experiment</h3> Four NILs previously generated from a cross of the resistant spring wheat line CM-82036 and Remus, a susceptible German spring wheat cultivar [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-

test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol Plant Pathol. 2013, 14: 772–785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e2726">14] were investigated in these experiments and also the resistant parent CM-82036. The NILs have been developed from one BC5F1 plant with Remus as the recurrent parent (5 backcrosses). In the BC5F2 lines that contain the resistance alleles from CM-82036 of both Fhb1 and Qfhs.ifa-5A (NIL1), or either Fhb1 (NIL2) or Qfhs.ifa-5A (NIL3) or none (NIL4) have been selected. F. graminearum conidia spores required for inoculation were produced on defined SNA medium under UV-light at 25°C. After two weeks conidia were harvested and diluted to 50,000 conidia/mL in water. Aliquots were stored at −80°C [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 10" title="Buerstmayr H, Steiner B, Hartl L, Griesser M, Angerer N, Lengauer D, Miedaner T, Schneider B, Lemmens M: Molecular mapping of QTLs for fusarium head blight resistance in spring wheat. II. Resistance to fungal penetration and spread. Theor Appl Genet. 2003, 107: 503–508. 10.1007/s00122-003-1272-6." href="/articles/10.1186/1471-2164-14-728#ref-CR10" id="ref-link-section-d51289e2745">10]. Plant growth conditions and the inoculation of flowering plants with F. graminearum spores were described previously [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 14" title="Schweiger W, Steiner B, Ametz C, Siegwart G, Wiesenberger G, Berthiller F, Lemmens M, Jia H, Adam G, Muehlbauer GJ, Kreil DP, Buerstmayr H: Transcriptomic characterization of two major fusarium resistance QTL, Fhb1 and Qfhs.ifa-5A, identifies novel candidate genes. Mol Plant Pathol. 2013, 14: 772–785. 10.1111/mpp.12048." href="/articles/10.1186/1471-2164-14-728#ref-CR14" id="ref-link-section-d51289e2754">14]. Briefly, 12 florets per head (from 6 central spikelets, the two basal florets) were inoculated at anthesis with 10 µl of a F. graminearum conidia spore suspension (500 conidia, concentration 50.000 conidia / mL) or mock by cautiously inserting a droplet onto the generative part of each floret without wounding the tissue. The treated heads were moistened with water and covered in plastic bags for 24 hours to provide humid conditions favorable for infection with the pathogen. Only palea and lemma of the inoculated florets were sampled including the respective part of the rachis. For each of the 60 samples (five genotypes, F. graminearum/mock treatment, two time points 30 and 50 hai, three replicates) 12 heads were used and pooled into one combined sample and stored at −80°C until use. <h3 class="c-article__sub-heading u-h3" id="Sec16">RNA-extraction and sequencing</h3> To eliminate RNases, metal jars with inherent metal spheres for Retsch-mill (MM 301, Haan, Germany) were sterilized at 180°C for 3 h and then stored at −80°C. All tissue belonging to one sample was pooled in one precooled jar and clamped in Retsch-mill. Grinding was performed for 30 seconds at full speed to obtain a fine tissue powder and immediately put back at −80°C. Total-RNA was extracted from 100 mg of frozen tissue powder using the RNeasy Plant Mini Kit (#74903, Qiagen, Venlo, Netherlands) according to manufacturer's instructions. The extracted RNA was checked for quality and quantity on an automated electrophoresis-system (Experion, #701-7000, Bio-Rad, Hercules, CA, US). Sequencing was performed on an Illumina HiSeq2000 machine using 8x multiplexing, theoretically generating 22 M reads per sample by the sequencing-provider GATC (Konstanz, Germany). The respective data sets are available in the EBI ArrayExpress (http://www.ebi.ac.uk/arrayexpress/) repository under the accession number E-MTAB-1729. <h3 class="c-article__sub-heading u-h3" id="Sec17">Data processing and mapping</h3> The recently published LCG wheat assembly [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 5" title="Brenchley R, Spannagl M, Pfeifer M, Barker GL, D'Amore R, Allen AM, McKenzie N, Kramer M, Kerhornou A, Bolser D, Kay S, Waite D, Trick M, Bancroft I, Gu Y, Huo N, Luo M-C, Sehgal S, Gill B, Kianian S, Anderson O, Kersey P, Dvorak J, McCombie WR, Hall A, Mayer FKX, Edwards KJ, Bevan MW, Hall N: Analysis of the bread wheat genome using whole-genome shotgun sequencing. Nature. 2012, 491: 705–710. 10.1038/nature11650." href="/articles/10.1186/1471-2164-14-728#ref-CR5" id="ref-link-section-d51289e2786">5] was used to identify RNA-Seq transcripts with Tophat and Cufflinks [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 24" title="Trapnell C, Roberts A, Goff L, Pertea G, Kim D, Kelley DR, Pimentel H, Salzberg SL, Rinn JL, Pachter L: Differential gene and transcript expression analysis of RNA-seq experiments with TopHat and cufflinks. Nat Protoc. 2012, 7: 562–578." href="/articles/10.1186/1471-2164-14-728#ref-CR24" id="ref-link-section-d51289e2789">24]. We removed one mock-treatment sample from genotype NIL2 (50 hai) as it did not pass quality control. Transcripts were

combined with Cuffcompare and were mapped against barley high confidence genes [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 18" title="Poland JA, Brown PJ, Sorrells ME, Jannink JL: Development of high-density genetic maps for barley and wheat using a novel two-enzyme genotyping-by-sequencing approach. PloS one. 2012, 7: e32253-10.1371/journal.pone.0032253." href="/articles/10.1186/1471-2164-14-728#ref-CR18" id="ref-link-section-d51289e2792">18] with Vmatch (http://www.vmatch.de) (exdrop = 3, seedlength = 12, hit length = 100 bp, identity > 85%) requiring a BBH and by taking the longest transcript of each reported gene loci. Transcripts with existing BBH to a barley gene served as input for network analysis and enrichment analyses. <h3 class="c-article__sub-heading u-h3" id="Sec18">Statistical analysis of differential gene expression</h3> Differentially expressed genes (DEG) were detected with Cuffdiff [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 24" title="Trapnell C, Roberts A, Goff L, Pertea G, Kim D, Kelley DR, Pimentel H, Salzberg SL, Rinn JL, Pachter L: Differential gene and transcript expression analysis of RNA-seq experiments with TopHat and cufflinks. Nat Protoc. 2012, 7: 562-578." href="/articles/10.1186/1471-2164-14-728#ref-CR24" id="ref-link-section-d51289e2813">24] between treatments in pair-wise comparisons. These were performed for samples from the same genotype but for different treatments or time-points. Thus we compared mock-inoculation against Fusarium-inoculation (M/F) at 30 hai and 50 hai. Additionally, we compared mock-inoculation at 30 hai with 50 hai (M/M). Cuffdiff default parameters were applied and the FDR-adjusted p-value was taken as a cut-off, keeping values below 0.1 as DEG. Genes that were significantly differentially expressed in M/M were not considered as differentially expressed in M/F comparison and vice versa. <h3 class="c-article__sub-heading u-h3" id="Sec19">Co-expression network and module detection</h3> Gene expression values (FPKM) were taken to infer a gene co-expression network. We used the log₂-transformed FPKM values, and replaced values smaller than one by zero. In order to keep only the most active genes we applied a coefficient of variation filter with a threshold of 1 across the different conditions. In order to infer a network, we made use of the WGCNA package [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 29" title="Langfelder P, Horvath S: WGCNA: an R package for weighted correlation network analysis. BMC bioinformatics. 2008, 9: 559-10.1186/1471-2105-9-559." href="/articles/10.1186/1471-2164-14-728#ref-CR29" id="ref-link-section-d51289e2833">29] with the soft-thresholding parameter beta set to 4 and absolute Pearson’s correlation coefficient. Thereby, we inferred an undirected, weighted network. Within the network, clusters of genes with similar expression patterns, so called modules, were then inferred using a clustering of the Topological Overlay Matrix (cutreeDynamic method; deepSplit = 2, minimal module size = 40, merging similar modules with parameter cut height = 0.2). The module eigengene (ME, [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 30" title="Langfelder P, Horvath S: Eigengene networks for studying the relationships between co-expression modules. BMC Syst Biol. 2007, 1: 54-10.1186/1752-0509-1-54." href="/articles/10.1186/1471-2164-14-728#ref-CR30" id="ref-link-section-d51289e2836">30]) of a given module is defined by the first principal component of the module expression matrix and can be regarded as the representative of the gene expression in a module [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 31" title="Langfelder P, Luo R, Oldham MC, Horvath S: Is my network module preserved and reproducible?. PLoS Comput Biol. 2011, 7: e1001057-10.1371/journal.pcbi.1001057." href="/articles/10.1186/1471-2164-14-728#ref-CR31" id="ref-link-section-d51289e2839">31]. By using the ME we could quantify the association between a module and the samples, with larger values indicating a stronger association with a module. <h3 class="c-article__sub-heading u-h3" id="Sec20">GO and interpro enrichment analyses</h3> GO terms and Interpro domains for the BBH transcripts were extracted from the barley repository (ftp://ftpmips.gsf.de/plants/barley/public_data/). GO enrichment analyses were performed using the topGO package [<a data-track="click" data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 26" title="Alexa A, Rahnenführer J, Lengauer T: Improved scoring of functional groups from gene expression data by decorrelating GO graph structure. Bioinformatics. 2006, 22: 1600-1607. 10.1093/bioinformatics/btl140." href="/articles/10.1186/1471-2164-14-728#ref-CR26" id="ref-link-section-d51289e2857">26], using Fisher’s exact test. To reduce the number of false positive findings the elim algorithm was applied and reported p-values smaller than 0.05 were kept for further analyses. Interpro terms were tested for enrichment using one-sided Fisher’s exact test, keeping Benjamini-Hochberg [<a data-track="click"

data-track-action="reference anchor" data-track-label="link" data-test="citation-ref" aria-label="Reference 25" title="Benjamini Y, Hochberg Y: Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Stat Methodol. 1995, 57: 289-300." href="/articles/10.1186/1471-2164-14-728#ref-CR25" id="ref-link-section-d51289e2866">25] adjusted p-values smaller than 0.05.
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773 <section aria-labelledby="Bib1"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Bib1">References</h2> <ol class="c-article-references"><li class="c-article-references__item js-c-reading-companion-references-item" itemprop="citation" itemscope="itemscope" itemtype="http://schema.org/ScholarlyArticle"><meta itemprop="author" content="CA. Cuomo, U. Guldener, JR. Xu, F. Trail, BG. Turgeon, A. Di Pietro, JD. Walton, LJ. Ma, SE. Baker, M. Rep, G. Adam, J. Antoniw, T. Baldwin, S. Calvo, Y-L. Chang, D. DeCaprio, KR. Gale, S. Gnerre, RS. Goswami, K. Hammond-Kosack, LJ. Harris, K. Hilburn, JC. Kennell, S. Kroken, JK. Magnuson, G. Mannhaupt, E. Mauceli, H-W. Mewes, R. Mitterbauer, G. Muehlbauer, " /><meta itemprop="datePublished" content="2007" /><meta itemprop="headline" content="Cuomo CA, Guldener U, Xu JR, Trail F, Turgeon BG, Di Pietro A, Walton JD, Ma LJ, Baker SE, Rep M, Adam G, Anto" />1. Cuomo CA, Guldener U, Xu JR, Trail F, Turgeon BG, Di Pietro A, Walton JD, Ma LJ, Baker SE, Rep M, Adam G, Antoniw J, Baldwin T, Calvo S, Chang Y-L, DeCaprio D, Gale KR, Gnerre S, Goswami RS, Hammond-Kosack K, Harris LJ, Hilburn K, Kennell JC, Kroken S, Magnuson JK, Mannhaupt G, Mauceli E, Mewes H-W, Mitterbauer R, Muehlbauer G, et al: The Fusarium graminearum genome reveals a link between localized polymorphism and pathogen specialization. Science. 2007, 317: 1400-1402. 10.1126/science.1143708. <ul class="c-article-references__links u-hide-print">
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848 Supporting data
849 The data set supporting the results of this article is available in the ArrayExpress repository (http://www.ebi.ac.uk/arrayexpress), accession number E-MTAB-1729. </section><section aria-labelledby="author-information"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="author-information">Author information</h2> Author notes<ol class="c-article-author-information__list">
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<li class="c-article-author-affiliation__authors-item"> & Klaus FX Mayer
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wheat fl-cDNA. (DOCX 21 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 3: Fusarium graminearum mapped read counts. Mapping of RNA-seq against Fusarium graminearum genes. (DOCX 13 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 4: Comparison of Fusarium graminearum mapped reads. Statistical overview of mapped reads against Fusarium graminearum per sample and condition. (DOCX 14 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 5: List of differentially expressed genes. A summary of differentialy expressed genes. (XLS 2 MB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 6: Enrichment analyses of DEG at 30 hai. Results of GO and Interpro enrichment analyses for DEG at 30 hai. (XLSX 186 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 7: Enrichment analyses of DEG at 50 hai. Results of GO and Interpro enrichment analyses for DEG at 50 hai. (XLSX 192 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 8: Module inference. Colored dendrogram showing the modules as inferred from the co-expression network. (DOCX 42 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 9: Gene module membership. The module membership of the analyzed genes as well as the contig mapping information. (XLS 405 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 10: Module eigengenes. Summary of the module eigengenes. (DOCX 25 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 11: Enrichment analyses for modules. Results of GO and Interpro enrichment

analyses for modules B, G, and H. (XLSX 181 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 12: DEG in submodules of module B. Similar to Figure <a data-track="click" data-track-label="link" data-track-action="figure anchor" href="/articles/10.1186/1471-2164-14-728#Fig2">2 the ratio of DEG in the submodules of module B is depicted. (DOCX 48 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 13: Enrichment analyses for modules of module B. Results of GO and Interpro enrichment analyses for module B submodules 1 and 2. (XLSX 11 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 14: Enrichment analyses for central genes. Results of GO and Interpro enrichment analyses for central genes. (XLSX 182 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 15: Differentially expressed central genes. Differentially expressed central genes and annotations with frequently observed GO terms. (XLSX 537 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 16: Regulation of NBS-LRR genes at different time points. The line-specific regulation of NBS-LRR genes at different time points. (PDF 133 KB)</h3> <h3 class="c-article-supplementary__title u-h3">Additional file 17: Regulation of glucanases at different time points. The line-specific regulation of glucanases at different time points. (PDF 133 KB)</h3> </section><section aria-labelledby="Sec22"> <h2 class="c-article-section__title u-h2 js-section-title js-c-reading-companion-sections-item" id="Sec22">Authors' original submitted files for images</h2> Below are the links to the authors' original submitted files for images. <h3 class="c-article-supplementary__title u-h3">Authors' original file for figure 1</h3> <h3 class="c-article-supplementary__title u-h3">Authors' original file for figure 2</h3> <div class="c-article-supplementary__item"

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889 BMC Genomics 14, 728 (2013). https://doi.org/10.1186/1471-2164-14-728 <a data-test="citation-link" data-track="click" data-track-action="download article citation" data-track-category="article body" data-track-label="link" href="/articles/10.1186/1471-2164-14-728.ris">Download citation<svg width="16" height="16" class="u-icon"><use xmlns:xlink="http://www.w3.org/1999/xlink" xlink:href="#global-icon-download"></use></svg> <ul class="c-bibliographic-information__list" data-test="publication-history"><li class="c-bibliographic-information__list-item"> Received: <time datetime="2013-06-25">25 June 2013</time> <li class="c-bibliographic-information__list-item"> Accepted: <time datetime="2013-10-14">14 October 2013</time> <li class="c-bibliographic-information__list-item"> Published: <time datetime="2013-10-24">24 October 2013</time> <li class="c-bibliographic-information__list-item c-bibliographic-information__list-item--doi"> <abbr title="Digital Object Identifier">DOI</abr>: https://doi.org/10.1186/1471-2164-14-728 <h3 class="c-article__sub-heading u-h3">Keywords</h3><ul class="c-article-subject-list"><li class="c-article-subject-list__subject">
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1153        <symbol id="global-icon-download" viewBox="0 0 16 16">
1154            <path d="M2 14c0-.556.449-1 1.002-1h9.996a.999.999 0 110 2H3.002A1.006 1.006 0 012 14zM9 2v6.8l2.482-2.482c.392-.392 1.022-.4 1.403-.02a1.001 1.001 0 010 1.417l-4.177 4.177a1.001 1.001 0 01-1.416 0L3.115 7.715a.991.991 0 01-.016-1.4 1 1 0 011.42.003L7 8.8V2c0-.55.444-.996 1-.996.552 0 1 .445 1 .996z" fill-rule="evenodd"/>
1155        </symbol>
1156        <symbol id="global-icon-email" viewBox="0 0 18 18">
1157            <path d="M1.995 2h14.01A2 2 0 0118 4.006v9.988A2 2 0 0116.005 16H1.995A2 2 0 010 13.994V4.006A2 2 0 011.995 2zM1 13.994A1 1 0 001.995 15h14.01A1 1 0 0017 13.994V4.006A1 1 0 0016.005 3H1.995A1 1 0 001 4.006zM9 11L2 7V5.557l7 4 7-4V7z" fill-rule="evenodd"/>
1158        </symbol>
1159        <symbol id="global-icon-institution" viewBox="0 0 18 18">
1160            <path d="M14 8a1 1 0 011 1v6h1.5a.5.5 0 01.5.5v.5h.5a.5.5 0 01.5.5V18H0v-1.5a.5.5 0 01.5-.5H1v-.5a.5.5 0 01.5-.5H3V9a1 1 0 112 0v6h8V9a1 1 0 011-1zM6 8l2 1v4l-2 1zm6 0v6l-2-1V9zM9.573.401l7.036 4.925A.92.92 0 0116.081 7H1.92a.92.92 0 01-.528-1.674L8.427.401a1 1 0 011.146 0zM9 2.441L5.345 5h7.31z" fill-rule="evenodd"/>
1161        </symbol>
1162        <symbol id="global-icon-search" viewBox="0 0 14 14">
1163            <path d="M13.545 12.648a.641.641 0 01.006.903.646.646 0 01-.903-.006l-2.664-2.663a6.125 6.125 0 11.897-.898l2.664 2.664zm-7.42-1.273a5.25 5.25 0 100-10.5 5.25 5.25 0 000 10.5z"></path>
1164        </symbol>
1165
```

```
    </svg>


<script data-test="app-bundle">
    (function() {
        if (window.config && window.config.mustardcut) {
            var appScript = document.createElement('script');
            appScript.src = '/static/app-bmc/js/app-bundle-866995bd4a.js';
            appScript.async = false;
            document.body.appendChild(appScript);
        }
    })();
</script>









    <script>
        window.Component = {};
    </script>
    <script src="/static/js/global-article-bundle-652d5d4cc5.js"></script>


    </body>
</html>
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