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**Something Something Something**

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**ABSTRACT**

**INTRODUCTION**

**RESULTS**

**eQTL indicate polygenic transcriptome modulation**

We performed genome-wide association (GWA) for eQTL detection across all genes expressed in the *B. cinerea* - *A. thaliana* pathosystem, including transcripts from the host and from the pathogen. To perform genome-wide association (GWA) and identify expression quantitative trait loci (eQTL) for both host and pathogen, we associated the expression profiles of these 9,267 *B. cinerea* genes and 23,947 *A. thaliana* genes to genome-wide SNP variation in the *B. cinerea* genome. We used a previous genome-wide SNP dataset that has XX SNPs with a minimum minor allele frequency of YY {Atwell 2018}. We performed Genome-wide Efficient Mixed Model Association (GEMMA) (Zhou and Stephens 2012) to rapidly estimate the significance of all markers for each expression profile. We first controlled for the effects of population structure within our *B. cinerea* isolates by calculating and including a relatedness matrix in the downstream analysis. GEMMA estimates the significance of effects of each SNP on the focal trait as a p-value. To determine significance of SNP effects across tens of thousands of traits (individual expression profiles in *B. cinerea* and *A. thaliana*), we permuted each trait across the 96 B. cinerea isolates five times, and repeated GEMMA analysis for each. We calculated the minimum p-value per SNP per transcript across these five permutations and used this to threshold our data. However, we found this approach overly conservative due to the magnitude of variation from one trait to another.

For individual expression traits, we find 0 to XX loci with significant p-values under XX for *B. cinerea*, and 0 to XX loci for *A. thaliana* transcripts (Figure N1). In total, genetic variation in *B. cinerea* appeared to significantly affect the expression of X *A. thaliana* genes and X *B. cinerea* genes. Overall, we find a highly polygenic basis of loci modulating transcriptome variation.

**Randomization to define hotspots**

To validate SNPs as significantly associated with transcript variation, we performed a comparative analysis of randomized phenotypes. Taking each transcriptional profile, we randomized the assignment of phenotypes across the 96-isolate collection. This analysis includes 9,267 randomized *B. cinerea* phenotypes and 23,947 randomized *A. thaliana* phenotypes, one from each measured expression profile. We repeated this randomization in a 5x permutation. We ran GEMMA on each of these permutations, and plotted SNP p-value vs. position (Figure N5). Permutation approaches are often more effective than p-value thresholding for determining significance across GWA studies with many phenotypes {CITE}.

**Absence of transcriptome cis-effect dominance**

Previous eQTL mapping studies using both GWA or structured mapping populations in a wide range of species show a dominance of loci that map to the gene itself, i.e. *cis-*eQTL {CITE}. To test if the Botrytis transcriptome shows a similar cis-eQTL predominance, we looked for a *cis*-diagonal signature of associations between transcript center and GWA SNP hits. We first focused on the single top SNP hit per transcript, with the highest probability (lowest p-value) of significant effect on expression in the gene of interest. If control of gene expression is localized to the gene itself or toproximate loci, we would expect a strong linear (*cis*-diagonal) association between the center of each gene and the genomic location of its top SNP hit. However, we find that few genes have a top SNP hit within the same chromosome, and even fewer within 1Mb (Figure N2). We conclude that most of this genetic variation is *trans*-acting, as we do not see a strong *cis*-diagonal signal when comparing transcript center to top SNP hit. This pattern holds whether we examine the top 1 SNP per transcript (Figure N2a) or the top 10 SNPs per transcript (FigureN2b). Further, we do visualize vertical stripes of SNPs, indicative of *trans*-eQTL hotspots; loci which modulate expression variation across many of the pathogen genes (Figure N2).

In these genome-wide transcript-to-SNP associations, we find that *cis*- control of gene expression is largely drowned out by patterns of *trans*-acting variation. To further search for a signature of dominant cis-effects, we calculated the distance between the center of each transcript and the top associated SNP. If *cis*- acting loci contribute the bulk of genetic control of expression variation, we would expect to see a high frequency of short-distance associations, and a rapid decline to a plateau moving away from the gene of interest. However, we observe that distances between transcript center and top SNP as far as 2 Mb are common (Figure N3). These distances are similar to those from the association of random transcript profiles to top SNPs (Figure SX1). As such, we do not see evidence for *cis*-effect loci overrepresented in the top candidates for control of expression variation. Rather, most control of gene expression variation in *B. cinerea* on *A. thaliana* appears to be *trans*-acting.

**Search for cis effects through focus on gene networks with presence-absence polymorphism**

The absence of a dominant signal for *cis*-eQTL could arise from *B. cinerea* having a different pattern of causal eQTL variation from our expectation. Alternatively, this could arise from *B. cinerea* having a sufficiently high genetic diversity that leads to false-negatives due to complex haplotype structures at causal loci (CITAITON). To test between these possibilities, we narrowed our focus to a set of three biosynthetic pathways that exist as gene clusters and have known presence-absence polymorphisms. to identify the role of *cis*-eQTL. These biosynthetic pathways contribute to *B. cinerea* virulence and the botcynic acid biosynthetic pathway (13 genes, 55.8 kb), botrydial biosynthetic pathway (7 genes, 26 kb), and a putative cyclic peptide pathway (10 genes, 46.5 kb) (Zhang, Corwin et al. 2018). Critically, the transcripts within each of these pathways are highly correlated across the isolates suggesting that their genetic variation is controlled by pathway-specific variation {Zhang 2018}. None of the genes showed a *cis*-eQTL within the GWA suggesting that the identified causal variation is solely in *trans* to the pathways.

To test if this result may be complicated by the architecture of the pathway loci, we initially focused on the botcynic acid biosynthesis network, which is known to have presence-absence polymorphisms in the species. We obtained all of the SNPs for this biosynthetic cluster and conducted an alignment of the *B. cinerea* isolates. This showed evidence of a number of distinct haplotypes with some relatively isolated isolates (e.g. B05.10, Fd1) (Figure N4a). Looking at the expression of the transcripts for the biosynthetic pathway showed a single clade that had a distinctly lower level of expression than the other clusters. Using SNP-level variation surrounding genes in this pathway showed that these 12 isolates share a 53.5 kbp deletion that removes the entire biosynthetic cluster(Figure N4c). We then tested if the remaining clusters had any link to transcript expression by by performing ANOVA across the 3 major clusters (1, 4, 5) . After removing the major deletion, we found no remaining significant effect of cluster membership on expression profile (F(1,74)=0.36, p=0.55). Although within each of these clusters there are independent isolates with low pathway expression polymorphisms (Noble Rot, 01.04.03, Apple 517, 02.04.09) (Figure N4b), these isolates each contain smaller independent deletions that likely abolish expression of the botcynic acid biosynthetic pathway (Figure N4c). This suggests that for this locus, there is a major *cis*-effect deletion and a number of rarer additional deletions that control expression variation. However, this *cis*-effect is not captured by the SNP-level data utilized for the GWA. Rather, our GWA analysis misses the major *cis*-eQTL signal of the network deletion. If insertion and deletion events account for the majority of localized control of expression variation, our GWA analysis will not detect these *cis*-effect loci. Thus, we investigated the other two biosynthetic pathways for additional evidence of *cis*-acting genetic variation.

The botrydial biosynthetic network, and the cyclic peptide pathway, exhibit similar cis-effect patterns to the botcynic acid biosynthetic network. Hierarchical clustering within each of these networks by genic SNP variation divides the isolate population into two groups, and mean pathway expression across all isolates is not differentiated by this clustering for either network (Figure S1, Figure S2). We find that SNP state does not detect the major cis-effects polymorphisms… We conclude that large cis effect loci exist for transcriptional regulation in this pathosystem, but that GWA across SNPs misses these patterns. This missing cis-effect likely amplifies the apparent magnitude of trans-acting loci.

**Detection and annotation of *trans*-eQTL hotspots**

Our 11 significant *trans­-*eQTL hotspots for *B. cinerea* range from 22 to 129 linked genes, with minimal overlap to expression modulation in *A. thaliana* (a maximum of 56 genes). These hotspots are dispersed across the genome, at least 0.1 Mb apart and across 9 chromosomes (Figure N7). The 11 significant cross-species *trans*-eQTL hotspots for *A. thaliana* are also dispersed across the genome of *B. cinerea*, covering 8 chromosomes with at least 0.1 Mb between hotspots (Figure N7). These range from 114 to 634 linked *A. thaliana* transcripts, with very low overlap with *B. cinerea* transcripts (a maximum of 3 genes).

The other typical predominant pattern in eQTL studies is the presence of hotspots, whereby variation in numerous transcripts links to specific loci. These are considered positions where there is a causal polymorphism that influences the regulation of numerous genes in *trans*, i.e. a *trans*-eQTL hotspot. In this dataset, we can extend this analysis to look for *trans*-eQTL hotspots that extend beyond *B. cinerea* and influence the expression of genes in the host, *A. thaliana*. To conduct a conservative search and to simplify the analysis, we focused on solely the single most-significant SNP (i.e. strongest evidence) that is linked to a given transcript. Taking these top SNPs for all *the B. cinerea* and *A. thaliana* transcripts, we queried for hotspots per transcriptome (Figure N6). By permuting the SNP positions, we identified maximum permuted hotspot sizes for *B. cinerea* as XX, and XX for *A. thaliana*. For further analysis of hotspots, we utilized a conservative threshold of 20 linked transcripts for *B. cinerea* and 150 transcripts for *A. thaliana*. This analysis identified 11 SNPs as potential *trans*-eQTL hotspots for the *B. cinerea* transcriptome and 11 SNPs as potential cross-species *trans*-eQTL hotSNPs influencing *the A. thaliana* transcriptome (Figure N6, Figure N7). The trans- eQTL hotspots are spread throughout the genome, present on chromosomes 2-6, 8-10, 12-15 (Figure N6). Hotspots were defined to the gene level, with 1 to X significant SNPs. One possibility is that a *trans*-eQTL hotSNP for *B. cinerea* transcripts may control virulence pathways and thus cause an associated *trans*-eQTL hotSNP in the *A. thaliana* response. To test for this, we looked for evidence of eQTL hotspots that are common across both *B. cinerea* and *A. thaliana* (Figure XX). We find that X% of hotspots are shared among both transcriptomes, X% are unique to *B. cinerea*, and X% are unique to *A. thaliana.* To test the dependency of these results on using solely the top SNP, we repeated the full analysis by selecting the top 10 SNPs per transcript. This again identified a limited number of *trans*-eQTL hotSNPs with little overlap between the two species transcriptomes (Table SX1; Figure SX3). This suggests that the pathogen’s influence on the host’s transcriptome is not solely limited to major interactions between *tran*s-eQTL hotSNPs but can involve more limited changes in the pathogen that are magnified in the host’s response.

To look for *B. cinerea* loci that are *trans*-acting to control expression variation in the affected host, we also examined patterns of association between *A. thaliana* expression variation and *B. cinerea* genomic variation. We identified hotspots putatively controlling *A. thaliana* expression variation for all *B. cinerea* chromosomes except 17 and 18 (Figure X4b). These *B. cinerea* loci may contribute to regulation of gene expression in the host.

**Annotation of eQTL hotspots**

We annotated the genes at these eQTL hotspots with functional information, including links to coexpression networks from previous RNAseq analysis of these transcripts (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018) (Table X1). eQTL hotspots linked to these coexpression networks could indicate regulatory points for these modules of expression variation.

Among the 11 *B. cinerea* hotspot *trans-*eQTL, three of these hotspot genes are linked to lesion size variation across all tested *A. thaliana* genotypes. A fourth gene is linked to lesion size variation on Col-0 *A. thaliana*. This gene is also linked to the major vesicle/ virulence network of *B. cinerea* coexpression on Col-0 *A. thaliana* (Zhang, Corwin et al. 2018). Nine of the 11 *B. cinerea* eQTL hotspots were also linked to genes in one or more of four major *B. cinerea* coexpression networks on *A. thaliana* (Figure N8). In particular, two of these were host-specific networks functionally associated with virulence; in total, 7 of the 11 *B. cinerea* eQTL hotspots was associated with one of these virulence coexpression networks. As such, we hypothesize that these major points of *B. cinerea* gene expression modulation may also exhibit regulation of virulence strategies on *A. thaliana*.

Among the 11 *A. thaliana* hotspot trans-eQTL, two of these genes are correlated to *B. cinerea* lesion size across all tested *A. thaliana* genotypes, including immune pathway mutants. An additional gene is correlated with lesion size variation on Col-0 *A. thaliana*, and one on *coi1-1* *A. thaliana.*

Nine of the *A. thaliana* eQTL hotspots were also linked to genes in one or more of six major genotype-dependent *A. thaliana* coexpression networks when infected with *B. cinerea* (Figure N8). These networks are host genotype-dependent, and either contain genes pointing to network function in jasmonate and salicylic acid signaling processes and camalexin biosynthesis (Network I), or photosynthesis in the host (Network IV). We observe particularly strong links between 4 of the 11 eQTL hotspots of *B. cinerea* modulation of *A. thaliana* gene expression and immune networks in *A. thaliana* (Figure N8). These frequent links suggest that our eQTL hotspots may exhibit regulatory control over coexpressed modules of genes active in virulence interactions between *B. cinerea* and its host.

If these eQTL are modulating expression of many genes, and affecting lesion size, they may be major *B. cinerea* control points in the plant-pathogen interaction.

We further examined functional annotation of the genes linked to our eQTL hotspots, to hypothesize mechanisms of regulation by these hotSNPs.

Many of the *B. cinerea* genes targeted by the hotSNPs are enzymatic (34% of our list of annotated hotSNP target genes, 140/412) (Table N2).

**METHODS**

**Experimental design**

We used a previously described collection of *B. cinerea* genotypes that were isolated as single spores from natural infections of fruit and vegetable tissues collected in California and internationally (Atwell, Corwin et al. 2015, Zhang, Corwin et al. 2017, Fordyce, Soltis et al. 2018, Zhang, Corwin et al. 2018). We focused analysis on the *A. thaliana* accession Columbia-0 (Col-0), and all plants were grown as described in a previous study, with 4-fold replication of the full randomized complete block experimental design across two independent experiments (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). The original study included wildtype Col-0 A. thaliana hosts, as well as knockouts to the salicylic acid pathway (*npr1-1*) and to jasmonic acid sensitivity (*coi1-1*). Leaves were harvested 5 weeks after sowing, and inoculated in a detached leaf assay with spores of each of 96 *B. cinerea* isolates (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018).

**Expression analysis**

RNASeq libraries were prepared as previously described (Kumar, Ichihashi et al. 2012, Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). Briefly, we prepared mRNA from leaves frozen at 16 hours post inoculation, and pooled amplified, size-selected libraries into four replicate groups of 96 barcoded libraries. Sequencing was completed on a single Illumina HiSeq 2500 (San Diego, CA) lane as single 50bp reads at the U.C. Davis Genome Center- DNA Technologies Core (Davis, CA). Individual libraries were then separated by adapter index from fastq files, evaluated for read quality and overrepresentation (FastQC Version 0.11.3, www.bioinformatics.babraham.ac.uk/projects/), and trimmed (fastx, http://hannonlab.cshl.edu/fastx\_toolkit/commandline.html). Reads were aligned to the *A. thaliana* TAIR10.25 cDNA reference genome, followed by the *B. cinerea* B05.10 cDNA reference genome, and we pulled gene counts (Langmead, Trapnell et al. 2009, Li, Handsaker et al. 2009, Van Kan, Stassen et al. 2017, Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). We summed counts across gene models, and normalized gene counts as previously described (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018).

We used as input the model-adjusted means per transcript from previously published studies in the *A. thaliana* transcriptome and *B. cinerea* transcriptome (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). *A. thaliana* and *B. cinerea* transcript phenotypes were from least square means of normalized gene counts in a negative binomial generalized linear model (nbGLM) (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). We calculated linear models from the transcript data including the effects of isolate and host genotype. We z-scaled all transcript profiles prior to GWA.

**Genome wide association**

For GEMMA mapping, we used 95 isolates with a total of 237,878 SNPs against the *B. cinerea* B05.10 genome (Atwell, Corwin et al. 2018). We used haploid binary SNP calls with MAF > 0.20 and <20% missingness. We ran GEMMA once per phenotype, across 9,267 *B cinerea* gene expression profiles and 23,947 *A. thaliana* gene expression profiles.

**Permutation and defining hotspots**

We plotted the number of transcripts linked to each SNP, summed across all 5 permutations, to calculate permuted hotspot size. For any SNPs that linked to permuted hotspots of over 5 transcripts in *B. cinerea* or 20 transcripts in *A. thaliana*, we removed these SNPs from further analysis as likely false positives. We then conservatively defined actual hotspots as SNP peaks exceeding 20 transcripts in *B. cinerea* and 150 transcripts in *A. thaliana*. We then collapsed hotspots into genes, such that all SNPs were annotated to the nearest gene within a 2kb window. The average LD decay in the B. cinerea genome is < 1kb, so we can be relatively confident of SNPs tagging particular genes at the hotspot peaks {Atwell 2018}.

**Annotation of gene ontology and network membership**

*A. thaliana* coexpression analysis identified 131 genes across four major networks {Zhang 2017}. Network architecture varied by plant host, but a constitutive core was conserved across *A. thaliana* genotypes. We compared our eQTL hotspots (both the gene at eQTL hotspot SNP and all associated transcript profiles) to the largest *A. thaliana* network lists (*npr1-1* background) to estimate all possible regulatory ties. We identified gene overlap with two of the major networks; Network I, camalexin biosynthesis; Network IV, chloroplast function.

**Pathway focus**

We focused further *cis*-effects analysis on three networks which were highly conserved across *B. cinerea* isolates (Zhang, Corwin et al. 2018). We clustered isolates by SNP data within focal networks. Hierarchical clustering was computed using the R package pvclust based on mean linkage (UPGMA), with correlation distance and 1000 bootstrap replications (Suzuki and Shimodaira 2015). AU p-values are reported in red, BP values in green. Edges with high AU values are considered strongly supported by the data, and clustering is drawn according to these edges with AU > 95%.

For botcynic acid biosynthesis, the major deletion extends 53.5 kb and includes SNP 4kb from the 5’ end of the chromosome, indicating a teleomeric loss on chromosome 1. We selected a focal region encompassing the deletion endpoints (1.4029, 1.82614) and an additional 2 genes beyond the deletion boundaries (Bcin01g00170, Bcin01g00190) (Figure N4c). We removed 10 SNPs that were likely miscalled (SNP state ~ inverse compared to surrounding region) and called all SNPs within the deletion region as missing.

**TABLE LEGENDS**

**Table N1. Annotation of the hotSNPs identified from *B. cinerea* and *A. thaliana* eQTL.**

**Table N2. Annotation of the *B. cinerea* genetic targets of *B. cinerea* hotSNPs.**

**Table N3. Annotation of the *A. thaliana* genetic targets of *B. cinerea* hotSNPs.**

**FIGURE LEGENDS**

**Figure N1. Manhattan plot examples for 1 transcript per species.** Panel a is an example plot of p-values for all *B. cinerea* SNP associations to a single *B. cinerea* transcript, from Bcin01g00170. Panel b is an example plot of p-values for all *B. cinerea* SNP associations to a single *A. thaliana* transcript.

**Figure N2. *cis*-diagonal plot comparing *B. cinerea* gene center to position of top associated SNP, for all 9,284 transcripts.** We retained only the SNPs with highest probability (lowest p-value) of significant effect on expression for each transcript. Panel a depicts the single top SNP per transcript. Panel b depicts the top 10 SNPs per transcript. Chromosomes are delimited by red bars along the x-axis. Vertical striping of SNP positions indicate genomic locations of putative *trans*-eQTL hotspots.

**Figure N3. Distance between transcript center and top SNP location for all *B. cinerea* expression profiles on Col-0 *A. thaliana*.** Data include the top 1 SNP identified by GEMMA association with each transcript expression profile (lowest p-value for association). Distances are in Mb, including only top SNPs on the same chromosome as the focal gene.

**Figure N4. *cis*-effect analysis of the botcynic acid biosynthetic gene network.** Panel a is hierarchical clustering of *B. cinerea* isolates from SNPs within the botcynic acid biosynthetic gene network. Clustering was based on mean linkage (UPGMA), with correlation distance and 1000 bootstrap replications. AU p-values are reported in red, BP values in green. Edges with high AU values are considered strongly supported by the data, and clustering is drawn according to these edges with AU > 95%. Panel b is Violin plots of botcynic acid network-level expression within *B. cinerea* clusters. Isolates are clustered based membership in groups defined by hierarchical clustering of the SNPs within the botcynic acid biosynthesis network (Figure X5). Panel c is the gene models of the biosynthetic gene network, with the cluster 3 deletion indicated as a triangle.

**Figure N5. Manhattan-type plot of GEMMA results of transcriptome-wide *B. cinerea* expression phenotypes.** Panel a is a Manhattan-type plot of the top 1 SNP hit per *B. cinerea* transcript on Col-0 *A. thaliana*. Panel b is a Manhattan-type plot of the top 1 SNP hit per *A. thaliana* transcript when infected by *B. cinerea*.

**Figure N6. All eQTL hotspots across the *B. cinerea* and *A. thaliana* transcriptomes.** We counted the number of genes (transcripts) associated with each SNP. Panel a is for all *B. cinerea* transcripts, panel b is all *A. thaliana* transcripts.

**Figure N7. Interspecific hotspot comparison on the *B. cinerea* genome.** For each SNP that is a top hit for one or more transcripts, the number of associated transcripts is counted, across both the *B. cinerea* transcriptome and the *A. thaliana* transcriptome.

**Figure N8. Genes linked to eQTL hotspots are in virulence and defense coexpression networks.** Circles along the *B. cinerea* genome map are hotspots, centered at the gene containing the eQTL and with radius proportional to the number of transcripts linked to this hotspot. eQTL for *B. cinerea* transcripts are drawn in blue, eQTL for *A. thaliana* transcripts are drawn in green. Links between hotspots and coexpression networks are drawn according to the number of genes shared between them, with variable widths; 2 pixels for 1 to 5 genes shared, 5 pixels for 6 to 10 genes, 10 pixels for 11 to 19 genes, 15 pixels for 20 to 114 genes.

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