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12 **Title: Interactions of tomato and *Botrytis* genetic diversity: Parsing the**

13 **contributions of host differentiation, domestication and pathogen variation**

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15 Short title: Interactions of tomato and Botrytis genetics

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Abstract

      While the impacts of crop domestication on specialist pathogens are well-studied, less is known about the interaction of crop variation and generalist pathogens. To study how genetic variation within a crop impacts plant resistance to generalist pathogens, we infected a collection of wild and domesticated tomato accessions with a genetically diverse population of the generalist pathogen *Botrytis cinerea*. We quantified variation in lesion size of 97 *B. cinerea* genotypes (isolates) on 6 domesticated *Solanum lycopersicum* and 6 wild *S. pimpinellifolium* genotypes. Lesion size was significantly affected by large effects of the host and pathogen's genotype, with a much smaller contribution of domestication. This pathogen collection also enables genome-wide association (GWA) mapping in *B. cinerea*. GWA in the pathogen showed that virulence is highly polygenic and involves a diversity of mechanisms. Breeding against this pathogen would likely need to utilize diverse isolates to capture all possible mechanisms. Critically, we identified a subset of *B. cinerea* genes where allelic variation was linked to altered virulence against the wild versus domesticated tomato, as well as loci that could handle both groups. This generalist pathogen already has a large collection of allelic variation that must be considered when designing a breeding program.

Introduction

      Plant disease is mediated by complex interactions among diverse host and pathogen molecular pathways, and the disease outcome is the sum of host plant susceptibility/resistance and pathogen virulence/sensitivity mechanisms. The specific outcome of any interaction is highly dependent on the genetic variation within these pathways in both the host and pathogen. Over time, mutation and selection have led to distinct genetic architectures in the host and pathogen that are at least partly influenced by the host range of the pathogen. Specialist pathogens are a major focus in plant pathology; virulent on a narrow range of hosts, and often limited to a single species or genus. Most known plant genes for resistance to specialist pathogens confer qualitative resistance through innate immunity via large-effect loci that enable the recognition of the pathogen (Dangl and Jones 2001, Jones and Dangl 2006, Dodds and Rathjen 2010,

52   Pieterse, Van der Does et al. 2012). These recognition signals can be conserved

53   pathogen patterns such as cell-wall polymers or flagellin, or alternatively, specific

54   virulence factors that block perception of the pathogen, and in turn are detected by plant

55   proteins that guard the signaling networks (Jones and Dangl 2006, Bittel and Robatzek

56   2007, Ferrari, Galletti et al. 2007, Boller and He 2009, Dodds and Rathjen 2010). The

57   evolution of large-effect qualitative loci has partly been driven by the narrow host range

58   for the pathogen that enhances co-evolution between host resistance genes and

59   pathogen virulence mechanisms.

60   In contrast to specialist pathogens, generalist pathogens are virulent across a

61   wide range of plant host species. Generalist pathogens potentially have less stringent

62   co-evolution to specific hosts and their accompanying resistance mechanisms, because

63   these pathogens can easily shift to new hosts in the environment. This allows generalist

64   pathogens to evade the rapid evolution of new resistance mechanisms within specific

65   hosts until they evolve to counter this new resistance. This niche-shifting ability may

66   partially explain the observation that most natural resistance to generalist pathogens is

67   highly polygenic, and the underlying plant genes for resistance are quantitative

68   (Glazebrook 2005, Nomura, Melotto et al. 2005, Goss and Bergelson 2006, Rowe and

69   Kliebenstein 2008, Barrett, Kniskern et al. 2009, Corwin, Copeland et al. 2016). Plant

70   quantitative resistance genes to generalist pathogens include a broad array of direct

71   defense genes, like those involved in secondary metabolite production, cell wall

72   formation, and defense proteins (Zhang, Khan et al. 2002, Denby, Kumar et al. 2004,

73   Zipfel, Robatzek et al. 2004, Ferrari, Galletti et al. 2007, Rowe and Kliebenstein 2008,

74   Poland, Balint-Kurti et al. 2009, Corwin, Copeland et al. 2016). Importantly, these

75   quantitative plant resistance loci do not alter resistance to all genotypes (isolates) of a

76   pathogen but interact with the infecting pathogen's genotype. For example, the ability of

77   the *Arabidopsis* defense metabolite, camalexin, to provide resistance to *Botrytis cinerea*

78   depends upon whether the specific isolate is sensitive or resistant to camalexin

79   (Kliebenstein, Rowe et al. 2005, Pedras and Ahiahonu 2005, Stefanato, Abou-Mansour

80   et al. 2009, Pedras, Hossain et al. 2011) and similarly *B. cinerea* virulence on tomato

81   varies with the isolate's ability to detoxify tomatine (Quidde, Osbourn et al. 1998,

82   Quidde, Büttner et al. 1999). In contrast to the polygenic nature of plant resistance to

83   generalist pathogens, little is known about the genetic architecture of virulence within
84   generalist pathogens, and how this is affected by genetic variation in the plant (Bartoli
85   and Roux 2017). There are no reported naturally variable large-effect virulence loci in
86   generalist pathogens, suggesting that virulence in generalist pathogens is largely
87   quantitative and polygenic. This potential for interaction between polygenic virulence in
88   generalist pathogens and equally polygenic resistance in host plants suggests that we
89   need to work with genetic variation in both the host and pathogen to truly understand
90   quantitative host-pathogen interactions.
91   Domestication of crop plants is a key evolutionary process in plants that has
92   affected resistance to specialist pathogens. Domesticated plant varieties are typically
93   more sensitive to specialist pathogens than their wild relatives (Smale 1996, Rosenthal
94   and Dirzo 1997, Couch, Fudal et al. 2005, Dwivedi, Upadhyaya et al. 2008), and
95   pathogens may evolve higher virulence on domesticated hosts (Stukenbrock and
96   McDonald 2008). Further, domestication typically imposes a genetic bottleneck that
97   reduces genetic diversity in the crop germplasm, including decreased availability of
98   resistance alleles against specialist pathogens (Tanksley and McCouch 1997, Doebley,
99   Gaut et al. 2006, Chaudhary 2013). These general evolutionary patterns, of reduced
100 resistance and allelic diversity found when studying the interaction of specialist
101 pathogens with crop plants, are assumed to hold for generalist pathogens and their
102 domesticated hosts. However, there is less information about how crop host
103 domestication affects disease caused by generalist pathogens, when the resistance to
104 these pathogens is quantitative and polygenic rather than qualitative and monogenic. As
105 such, there is a need to quantify the effect of domestication on a broad generalist
106 pathogen in comparison to the rest of the crop's standing variation to test how and if
107 domestication influences the pathogen.
108   *Botrytis cinerea* provides a model generalist pathogen for studying quantitative
109 interactions with plant hosts and underlying evolutionary processes. *B. cinerea* is a
110 broad generalist pathogen that can infect most tested plants, from bryophytes to
111 eudicots, and causes wide ranging pre- and post-harvest crop losses (Nicot and Baille
112 1996, Elad, Williamson et al. 2007, Fillinger and Elad 2015). Individual isolates of *B.
113 cinerea* show the same broad host range (Deighton, Muckenschnabel et al. 2001,

114   Finkers, van Heusden et al. 2007, Ten Have, van Berloo et al. 2007, Corwin, Subedy et

115   al. 2016). This is in contrast to pathogens like *Fusarium oxysporum* where the species

116   can infect diverse hosts, but each isolate is highly host specific (Katan 1999, Ormond,

117   Thomas et al. 2010, Loxdale, Lushai et al. 2011, Barrett and Heil 2012). *B. cinerea*

118   isolates display significant variation in virulence phenotypes, partly due to genetic

119   variation in specific virulence mechanisms, like the production of the phytotoxins,

120   botrydial and botcinic acid (Siewers, Viaud et al. 2005, Dalmais, Schumacher et al.

121   2011). This genetic variation also influences cell wall degrading enzymes and key

122   regulators of virulence like *VELVET* that quantitatively control virulence on multiple host

123   plants (Rowe and Kliebenstein 2007, Schumacher, Pradier et al. 2012). This standing

124   diversity in virulence mechanisms can contribute to the formation of quantitative

125   differences in virulence between the isolates (Ten Have, Mulder et al. 1998). The

126   phenotypic variation is driven by a high level of sequence diversity spread across the

127   genome (Rowe and Kliebenstein 2007, Fekete, Fekete et al. 2012). The polymorphism

128   rate in *B. cinerea*, 37 SNP/kb, is much more variable than most previously studied plant

129   pathogens (1-2 SNP/kb in *Blumeria graminis*, 1.5 SNP/kb in *Melampsora larici-populina*,

130   5.5 SNP/kb in the compact genome of the obligate biotroph *Plasmodiophora brassicae*,

131   12.3 SNP/kb in the wheat stem rust pathogen *Puccinia graminis* f. sp. *tritici*) and human

132   pathogens (3-6 SNP/kb in *Mycobacterium tuberculosis)*. In addition to SNP diversity, the

133   genomic sequencing showed that *B. cinerea* has a high level of recombination and

134   genomic admixture, as if it were a randomly intermating population (Supplemental

135   Figure 1) (Atwell, Corwin et al. 2018). As such, a collection of *B. cinerea* isolates contain

136   genetic variation in a wide range of virulence mechanisms, offering the potential to

137   challenge the host with a blend of diverse virulence mechanisms to identify the

138   pathogen variation controlling quantitative virulence .

139   A model pathosystem for studying quantitative host-pathogen interactions is the

140   tomato-*B. cinerea* system, where the pathogen causes crop loss due to both pre- and

141   post-harvest infection (Dean, Van Kan et al. 2012, Hahn 2014, Romanazzi and Droby

142   2016). Resistance to *B. cinerea* is a quantitative trait in tomato as with most other

143   species, with identified tomato QTLs each explaining up to 15% of phenotypic variation

144   for lesion size on stems (Dıaz, ten Have et al. 2002, Finkers, van Heusden et al. 2007,

Ten Have, van Berloo et al. 2007, Rowe and Kliebenstein 2008, Corwin, Copeland et al.
2016). Tomato is also a key model system to study how domestication influences plant
physiology and resistance, including alterations in the circadian clock (Tanksley 2004,
Bai and Lindhout 2007, Panthee and Chen 2010, Bergougnoux 2014, Müller, Wijnen et
al. 2016), which can modulate resistance to *B. cinerea* (Sauerbrunn and Schlaich 2004,
Weyman, Pan et al. 2006, Bhardwaj, Meier et al. 2011, Hevia, Canessa et al. 2015).
This suggests that host plant diversity within tomato can alter traits known from other
systems to influence *B. cinerea* resistance. Tomato domestication is typically
considered a single event, followed by extensive crop improvement (Lin, Zhu et al.
2014, Blanca, Montero-Pau et al. 2015). Thus, we are using the tomato-*B. cinerea*
pathosystem to directly measure the interaction of domesticated crop variation with
genetic variation in a generalist pathogen to better understand the evolution of this
pathosystem.

In this study, we infected 97 genetically diverse *B. cinerea* isolates on a collection
of domesticated tomato, *S. lycopersicum*, and wild tomato, *S. pimpinellifolium*, and
quantified the interaction through lesion size in a detached leaf assay. Previous studies
have examined *B. cinerea* resistance between domesticated and wild tomato species
using single isolates of pathogens (Egashira, Kuwashima et al. 2000, Nicot, Moretti et
al. 2002, Guimaraes, Chetelat et al. 2004, Ten Have, van Berloo et al. 2007, Finkers,
Bai et al. 2008). These previous studies typically used individual wild and domesticated
tomato accessions that were the founders of mapping populations and found a wide
range of *B. cinerea* resistance. However, it is still unknown how domesticated and wild
tomatoes compare for *B. cinerea* resistance using multiple plant genotypes and a
population of the pathogen. We selected accessions to sample major geographic origins
of the progenitor species, and focused the domesticated germplasm on diverse mid- to
late- 20th century improved germplasm (Lin, Zhu et al. 2014, Blanca, Montero-Pau et al.
2015). In this study, we asked whether *B. cinerea* virulence was controlled by host
variation, pathogen variation, or the interaction between them. Lesion size of *B. cinerea*
is a quantitative trait that was controlled by plant domestication status, plant genotype
and pathogen isolate. Finally, we aimed to identify the genetic basis of variation in *B.
cinerea* virulence on *S. lycopersicum* and *S. pimpinellifolium*. We conducted genome-

176 wide association (GWA) in *B. cinerea* to identify pathogen loci where genetic variation

177 leads to altered virulence across the host genotypes, including a specific test for loci

178 that influence responses to crop domestication. Few studies have conducted GWA in

179 plant pathogens for virulence phenotypes, and most of these were limited by few

180 variable loci or few genetically distinct isolates (Dalman, Himmelstrand et al. 2013, Gao,

181 Liu et al. 2016, Talas, Kalih et al. 2016, Wu, Sakthikumar et al. 2017). Our previously-

182 sampled isolate collection includes genetic diversity across 272,672 SNPs

183 (Supplemental Figure 1) (Atwell, Corwin et al. 2015, Zhang, Corwin et al. 2017, Atwell,

184 Corwin et al. 2018). We found that the genetic architecture of virulence of *B. cinerea* is

185 highly quantitative, with hundreds of significant SNPs with small effect sizes associated

186 with lesion area on each tomato genotype. Importantly, there is a subset of loci in the

187 pathogen where allelic variation gives the isolates opposing responses to crop

188 domestication. These pathogen loci could provide tools for understanding how

189 domestication in tomato has influenced generalist pathogen resistance, to inform

190 breeding efforts.

191

192

Results

Experimental Design

      To measure how tomato genetic variation affects quantitative resistance to a population of a generalist pathogen, we infected a collection of 97 diverse *B. cinerea* isolates (genotypes) on wild and domesticated tomato genotypes. We selected 6 domesticated *Solanum lycopersicum* and 6 wild *S. pimpinellifolium* accessions, the closest wild relative of *S. lycopersicum*, to directly study how domestication has influenced resistance to *B. cinerea* (Peralta, Spooner et al. 2008, Müller, Wijnen et al. 2016)(Supplemental Figure 2). Our previously collected *B. cinerea* sample includes 97 isolates obtained from various eudicot plant hosts, including tomato stem tissue (2 isolates; T3, KT) and tomato fruit (3 isolates; KGB1, KGB2, Supersteak) (Atwell, Corwin et al. 2015, Zhang, Corwin et al. 2017, Atwell, Corwin et al. 2018). We infected all 97 *B. cinerea* isolates onto each of the 12 plant genotypes in 3-fold replication across 2 independent experiments in a randomized complete block design, giving 6 measurements per plant-pathogen combination, for a total of 3,276 lesions. Digital measurement of the area of the developing lesion provides a composite phenotype controlled by the interaction of host and pathogen genetics. This measurement of the plant-*B. cinerea* interaction has been used successfully in a number of molecular and quantitative genetic studies (Ferrari, Plotnikova et al. 2003, Denby, Kumar et al. 2004, Kliebenstein, Rowe et al. 2005, Ferrari, Galletti et al. 2007, Ten Have, van Berloo et al. 2007, AbuQamar, Chai et al. 2008, Rowe and Kliebenstein 2008, Liu, Hong et al. 2014). It should be noted that we are not focusing on MAMP or PAMP specific host/pathogen interactions with this study; we are instead allowing the identification of any mechanism that may influence the host/pathogen interaction including metabolism, development or any other unknown component. If there is genetic variation affecting the trait, and the trait influences the interaction of host and pathogen, it will be a component of the experiment. This fits with the recently developing view that growth, development and resistance in plants are highly integrated processes that may not be as distinct as once believed (Campos, Yoshida et al. 2016, Ballaré and Pierik 2017, Züst and Agrawal 2017, Izquierdo-Bueno, González-Rodríguez et al. 2018).

Lesion size (phenotypic) variation

We collected images of all lesions at 24, 48, and 72 hours post inoculation. At 24 hours, no visible lesions were present on the tomato leaves. At 48 hours, a thin ring of primary lesion became visible surrounding the location of the spore droplet, but no expansion was visible. At 72 hours significant lesion growth was visible, but no lesions had spread to infect over half of the leaflet. We digitally measured the area of all developing lesions at 72 hours post infection (HPI) as a measure of virulence (Figure 1). We use the linear measurement of lesion area for several reasons. First, in previous work 72 HPI *B. cinerea* lesion area growth appears to enter a relatively linear growth phase (Rowe, Walley et al. 2010). Secondly, previous research has shown that the linear measurement behaves as a normally distributed trait (Kliebenstein, Rowe et al. 2005, Corwin, Copeland et al. 2016, Atwell, Corwin et al. 2018, Fordyce, Soltis et al. 2018). And finally, previous work has shown that Botrytis isolates display large variation in their unit biomass per lesion area and as such growth in biomass is not the sole factor driving this measure (Corwin, Subedy et al. 2016). We observed a mean lesion size of 0.67 cm^2 across the full experiment, with 0.94 CV across the full isolate population on all tomato genotypes. Individual isolates were highly variable in their lesion size across tomato genotypes (Figure 1c-h), with mean lesion size per isolate of 0.14 cm^2 to 1.29 cm^2, and individual isolate coefficient of variation (CV) from 0.51 to 1.68 across all observations on all tomato genotypes (Supplemental Data Set 1). A subset of these isolates is highly virulent on tomato (mean lesion size > 1.05 cm^2, Figure 1e), and a subset can be considered saprophytic (mean lesion size < 0.3 cm^2, Figure 1f). Lesion size of *B. cinerea* on tomato showed a weak positive correlation with lesion size on *A. thaliana* from previous studies; both on domesticated tomato (r=0.247, p= 0.003) and on wild tomato (r=0.301, p= 0.016) (Supplemental Figure 3)(Zhang, Corwin et al. 2017). This lack of correlation suggests the presence of both shared and unique mechanisms of quantitative virulence in the two species.

Contribution of Pathogen Genetics and Plant Genetics Effects on Resistance

To measure the relative contribution of genetic diversity in the plant and the pathogen to variation in the virulence/ susceptibility phenotype, we used a general linear model (R

255 lme4 package;(Bates, Maechler et al. 2015)). This model directly tested the contribution

256 of pathogen genotype (isolate), plant genotype, and plant domestication status to

257 variation in lesion size. The final model showed that genetic variation within both the

258 host plant and the pathogen had significant effects on lesion growth, each explaining

259 approximately the same portion of the variance (Table 1 and Figure 1c). Interestingly,

260 while tomato domestication status significantly impacted *B. cinerea* virulence, it was to a

261 much lower level than the other factors (Table 1). There was no evidence for significant

262 interaction effects between pathogen isolate and plant genotype. Thus, the interaction

263 between tomato and *B. cinerea* was significantly controlled by genetic diversity within

264 the host plant and the pathogen, including a slight effect of domestication status.

265

266 **Table 1. ANOVA results of the interaction between 12 tomato accessions and 95**
267 ***B. cinerea* isolates measured as lesion area.**
268 Results of general linear modelling of lesion area for 12 tomato accessions by 95 *B.*
269 *cinerea* isolates is shown (R lme4 package version 1.1-18-1;(Bates, Maechler et al.
270 2015)). Two of our 97 isolates did not have replication across 2 experiments, so they
271 were dropped at this stage of analysis. The terms are as follows; Isolate is the 95 *B.*
272 *cinerea* isolates, Domestication is wild tomato, *S. pimpinellifolium*, versus domesticated
273 tomato, *S. lycopersicum*, Plant is 12 tomato genotypes nested within their respective
274 domestication groupings, Experiment tests the random effect of 2 independent replicate
275 experiments. The nested random effects of whole plant sampled, leaf sampled, and
276 leaflet pair are included. In addition, interactions of these factors are tested (:). The
277 degrees of freedom and p-value are shown. For fixed effects, the type II sum of squares
278 and F-value are shown, and for random effects the likelihood ratio test statistic (LRT) is
279 shown.

280

Fixed Effect	SS	F value	DF	p
Isolate	37.8	1.7	94	**0.007**
Domestication	3.4	14.1	1	**0.0006**
Domest/Plant	39.3	16.2	10	**5e-11**
Iso:Domest	15.8	0.7	94	0.99
Iso:Domest/Plant	179.1	0.8	940	1
Random Effect	LRT	DF	p	
1 | Experiment	136	1	**<2e-16**	
1 | Whole Plant	0.21	1	0.65	
1 | WP/Leaf	22.4	1	**2e-06**	
1 | WP/Leaf/Leaflet Pair	0	1	1	
1 | Exp:Iso	321	1	**<2e-16**	

281

Pathogen Specialization to Source Host

One evolutionary model of plant-generalist pathogen interactions suggests that pathogen isolates within a generalist species may specialize for interaction with specific hosts. Alternatively, generalist isolates may show no host specialization or preference. Our collection of *B. cinerea* includes five isolates that may be adapted to tomato, as they were collected from *S. lycopersicum*. To test if there is evidence for specialization to the source host, we compared the virulence of the *B. cinerea* isolates obtained from tomato to the broader pathogen population. For *B. cinerea* genotypes isolated from tomato tissue vs. other hosts, there was no significant difference in lesion size across all tomato genotypes (t-test; n = 97, p=0.14) (Figure 1g). In fact, one isolate collected from tomato tissue (KGB1) was within the 10 least-virulent isolates and another (Triple3) was within the 10 most-virulent isolates (Figure 1g). This demonstrated significant genetic variation in virulence across the *B. cinerea* isolates, and that this collection of *B. cinerea* isolates from tomato do not display a strong host-specificity for tomato (Martinez, Blancard et al. 2003, Ma and Michailides 2005, Rowe and Kliebenstein 2007, Samuel, Veloukas et al. 2012).

Pathogen Specialization to Host Genotype

Though we did not find evidence for *B. cinerea* preference for tomato based on isolate host source, the *B. cinerea* isolates may contain genetic variation at individual loci that allow them to better attack subsets of the tomato genotypes (Rowe and Kliebenstein 2007, Kretschmer and Hahn 2008, Corwin, Subedy et al. 2016). A visual analysis of the data suggested an interaction between the genomes of *B. cinerea* and tomato (Figure 1 c-h). However, when using the full model, we found no significant interaction between isolate and individual host genotype, even though there was a large fraction of variance within these terms (Table 1). This may indicate a lack of interaction between genetic variation in the host and pathogen. Interaction effects in large datasets can be difficult to identify using mixed models, so we used a second standard statistical approach, a Wilcoxon signed-rank test. We used model-adjusted lesion sizes as input to test if the rank of *B. cinerea* isolate-induced lesion size significantly changes between pairs of tomato genotypes. This showed that when using the full isolate population, the rank

313 performance of the isolates does significantly vary between host genotypes. When

314 comparing mean lesion size between paired plant genotypes, 59% (39 out of 66) of

315 tomato accession pairs had significantly different ranking of the isolates (Wilcoxon

316 signed-rank test with Benjamini-Hochberg FDR-correction, Table 2, Supplemental

317 Figure 4). A significant p-value indicates that the two host genotypes show evidence for

318 different virulence interactions with the population of *B. cinerea* isolates, providing

319 evidence for host x pathogen genotypic interactions. This pattern was consistent across

320 domesticated host pairs, wild host pairs, or between-species host pairs (Wilcoxon

321 signed-rank test with B-H FDR-correction, Table 2). This provides evidence that the

322 population of *B. cinerea* does display differential responses to the tomato genetic

323 variation.

324 To focus on whether specific *B. cinerea* isolates may be sensitive to tomato

325 domestication, we applied a Wilcoxon and ANOVA approach. Overall, most isolates

326 (78/97, 80%) are more virulent on domesticated than wild tomato (Figure 3;

327 Supplemental Data Set 1). Using a Wilcoxon signed-rank test to compare the rank of

328 model-corrected mean lesion size of all the *B. cinerea* isolates on wild versus

329 domesticated tomato we found a significant difference (Wilcoxon signed-rank test, W =

330 5801, p-value = 0.0007) (Figure 3). While this shows a general population behavior, we

331 used single-isolate ANOVAs to test if any specific pathogen genotypes had a significant

332 association with domestication. These general linear models included the fixed effects

333 of plant, domestication, and the random effect of experiment. After adjusting for multiple

334 testing, this identified two isolates (Fd2, Rose) with a significant effect of domestication

335 on lesion size (p < 0.05, FDR corrected) (Figure 1h), both of which are more virulent on

336 domesticated tomato (Supplemental Data Set 3).

337   To assess whether isolates could appear domestication-associated due to

338 random chance, we bootstrapped assignment of plant accessions to domestication

339 groups. 96 of the 100 bootstraps identified no isolates with domestication sensitivity,

340 and the other four bootstraps identified only 2 isolates showing significant domestication

341 association (FDR <0.01). Therefore, our individual isolate observations are in the 96th

342 percentile. While this is suggestive, a more precise estimate of isolate x domestication

interactions would require larger experiments using either more replication or additional plant genotypes.

Table 2. Rank order shifts of 97 *B. cinerea* isolates by lesion area across all of the tomato accessions.
Wilcoxon signed-rank test on comparing model-corrected mean *B. cinerea* lesion area on tomato accessions. This tests for a change in the rank order of the 97 isolates between each pair of tomato accessions. A significant p-value suggests that the relative performance of individual isolates is altered from one host to the other. The lower left corner of the chart includes B-H FDR-corrected p-values, the upper right corner includes the test statistic (W). Bold text indicates significance at p < 0.01 after correction, italicized text indicates suggestive p-values 0.01 < p < 0.1. NS shows non-significant interactions.

		Wild						Domesticated					
		LA1547	LA1589	LA1684	LA2093	LA2176	LA480	LA2706	LA3008	LA3475	LA410	LA4345	LA4355
Wild	LA1547		2978	3988	2927	1865	3008	1710	3460	1597	1135	3928	2944
	LA1589	<0.001		5401	4699	3359	4662	3014	4918	2938	2340	5536	4454
	LA1684	NS	*0.029*		3709	2552	3690	2296	4004	2205	1690	4537	3571
	LA2093	<0.001	NS	*0.049*		3013	4496	2732	4889	2588	1947	5534	4264
	LA2176	<0.001	**0.004**	<0.001	<0.001		5837	4029	6002	3963	3276	6706	5583
	LA480	<0.001	NS	*0.044*	NS	**0.001**		6143	4192	6286	6855	3575	4702
Domesticated	LA2706	<0.001	<0.001	<0.001	<0.001	NS	<0.001		6311	4523	3876	6917	5940
	LA3008	**0.009**	NS	NS	NS	<0.001	NS	<0.001		2619	2082	5100	4049
	LA3475	<0.001	<0.001	<0.001	<0.001	NS	<0.001	NS	<0.001		3815	7088	5984
	LA410	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	NS	<0.001	NS		7567	6602
	LA4345	*0.16*	*0.011*	NS	*0.011*	<0.001	*0.021*	<0.001	NS	<0.001	<0.001		3439
	LA4355	<0.001	**NS**	*0.02*	**NS**	0.008	**NS**	<0.001	**NS**	<0.001	<0.001	<0.001	

Domestication and Lesion Size Variation

360   Existing literature predominantly reports that crop domestication decreases plant

361   resistance to pathogens (Smale 1996, Rosenthal and Dirzo 1997, Couch, Fudal et al.

362   2005, Dwivedi, Upadhyaya et al. 2008, Stukenbrock and McDonald 2008). While we did

363   observe the expected decreased resistance (by 18%) in domesticated tomato (Figure 2

364   and 3, Table 1), domestication was a minor player in controlling lesion size variation,

365   with most of the plant genetic signature coming from variation within both the wild and

366   domesticated tomato species, contributing 12-fold more variation in resistance than

367   domestication alone (Table 1). Removing the two domestication-associated isolates

368   (Fd2, Rose) from our population did not eliminate the effect of tomato domestication on

369   lesion size, as it was still significant and *B. cinerea* was still more virulent on

370   domesticated tomato by 17% (Supplemental Table 1). To test how this mild

371   domestication effect might be sensitive to shifts in the collection of tomato genotypes,

372   we used the same bootstraps from above for the full model. Our observed

373   domestication effect was in the top 80th percentile across all bootstraps, suggesting that

374   while the domestication effect is small, it is relatively stable in response to shifts in the

375   genotypes. However, a larger sample of *S. lycopersicum* and *S. pimpinellifolium*

376   genotypes would be needed to develop a more precise estimate of any domestication

377   effect on lesion size.

378   In addition to altering trait means, domestication commonly decreases genetic

379   variation in comparison to wild germplasm due to bottlenecks, including for tomato

380   (Tanksley and McCouch 1997, Doebley, Gaut et al. 2006, Bai and Lindhout 2007). We

381   would expect this decreased genetic variation to limit phenotypic variation, including

382   disease phenotypes. Interestingly in this tomato population, we did not observe reduced

383   variation in lesion size in the domesticated tomato. The wild and domesticated tomato

384   genotypes showed similar variation in resistance (F-test, $F_{96,96}=1.39$, p=0.11) (Figure 3,

385   Supplemental Figure 2). Overall, there is a slight domestication impact on average

386   resistance to *B. cinerea*, and no evidence of a phenotypic bottleneck due to

387   domestication. This suggests that in the tomato-*B. cinerea* pathosystem, domestication

388   is not a major part of the variation.

389

390   **Quantitative Genetics of Pathogen Virulence on Tomato**

391   Genetic variation within *B. cinerea* had a large effect on virulence on tomato and

392   showed some evidence for interaction with tomato domestication (Table 1). This

393   suggests that there is genetic variation within the pathogen, in which some alleles

394   enhance, and other alleles decrease virulence depending upon the plant's genotype. To

395   identify variable pathogen genes controlling differential virulence across plant

396   genotypes, we conducted GWA mapping analysis within the pathogen, using 272,672

397   SNPs compared to the *B. cinerea* T4 reference genome (Supplemental Figure 1)

398   (Atwell, Corwin et al. 2018). Due to the large effect of plant genotype on resistance to *B.*

399   *cinerea*, we performed GWA using model-corrected least-squared mean virulence

400   measured on each tomato genotype as separate traits. We used a ridge-regression

401   approach (bigRR) to estimate the phenotypic effects across the genome (Shen, Alam et

402   al. 2013, Corwin, Copeland et al. 2016, Corwin, Subedy et al. 2016, Francisco, Joseph

403   et al. 2016, Atwell, Corwin et al. 2018). To determine significance of SNP effects under

404   GWA, we permuted phenotypes 1000 times to calculate 95, 99, and 99.9% effect size

405   thresholds within each plant host. At 1000 permutations, the 99.9% threshold is

406   imprecise, but we included this approximate threshold to identify conservative SNP

407   associations. GWA analysis showed that the genetic basis of *B. cinerea* virulence on

408   tomato is highly polygenic. Consistent with a polygenic structure of this trait in the

409   pathogen, GWA did not identify large-effect SNPs (Figure 4). The number of significant

410   *B. cinerea* virulence SNPs identified by this ridge-regression approach (bigRR) varied

411   by plant accession, from 1,284 to 25,421 SNPs on the 12 different host genotypes

412   (significance was determined by the SNP effect size estimate exceeding the 99% 1000-

413   permutation threshold).

414   At the SNP level, fewer loci contribute to virulence across all host genotypes. We

415   found five *B. cinerea* SNPs significantly linked to altered lesion size on all 12 tomato

416   accessions (Figure 4b). 215 SNPs were called in at least ten hosts, and 3,300 SNPs

417   were called in at least half of the hosts while 27% (46,000) of the significant SNPs were

418   linked to virulence on only a single host tomato genotype. These levels of overlap

419   exceed the expected overlap due to random chance (Figure 5a). While only a small

420   subset of these *B. cinerea* SNPs were linked to virulence on all the tomato genotypes,

421   we obtained better overlap across host genotypes by focusing on gene windows.

422   To focus on the small-effect genes linked to *B. cinerea* virulence, we classified a
423   gene as significantly associated if there was 1 SNP linked to a trait using a 2kbp window
424   surrounding the start and stop codon for a given gene. This analysis identified 14 genes
425   linked to differential virulence in all 12 tomato accessions by bigRR (Figure 5b,
426   Supplemental Data Set 2a), as some SNPs within a gene had accession-specific
427   phenotypes (significant in <12 tomato accessions). A further 1045 genes were linked to
428   differential virulence on 7 to 11 of the tomato accessions by bigRR (Figure 5b,
429   Supplemental Data Set 2a).
430   Of the 14 genes with SNPs significantly associated with *B. cinerea* virulence on
431   all tomato genotypes by bigRR, most have not been formally linked to pathogen
432   virulence. However, SNPs within a pectinesterase gene (BcT4_6001, Bcin14g00870)
433   were associated to virulence across 11 tomato accessions. Pectinesterases are key
434   enzymes for attacking the host cell wall, suggesting that variation in this pectinesterase
435   locus and the other loci may influence pathogen virulence across all the tomato
436   genotypes (Valette-Collet, Cimerman et al. 2003). Therefore, as an example of a
437   virulence gene identified by our GWA methods, we looked for evidence of multiple
438   haplotypes in this locus linked to virulence by visualizing the SNP effects across the
439   pectinesterase gene. We plotted the effect sizes for all SNPs in this gene and
440   investigated the linkage disequilibrium amongst these SNPs (Figure 6). This showed
441   that the effect of SNPs across this gene vary in effect direction depending on tomato
442   host genotype (Figure 6a). We identified two haplotype blocks contributing to the
443   association of this gene to the virulence phenotype (Figure 6b). One block is associated
444   with SNPs in the 5' untranslated region in SNPs 5-11, and the second block is SNPs
445   that span the entirety of the gene in SNPs 13-26. Interestingly, there are only two SNPs
446   in the open reading frame of the associated gene (Figure 6). This suggests that the
447   major variation surrounding this locus is controlling the regulatory motifs for this
448   pectinesterase. Thus, there is significant genetic variation in *B. cinerea* virulence that is
449   dependent upon the host's genetic background. This suggests that the pathogen relies
450   on polygenic small effect loci, potentially allowing selection to customize virulence on
451   the different tomato hosts.
452

453

Quantitative Genetics of Pathogen Response to Tomato Domestication

The identification of two isolates that differed on wild and domesticated tomato indicated that there may be some natural genetic variation in *B. cinerea* linked to this phenotypic variation. To directly map *B. cinerea* genes that control differential virulence on wild versus domesticated tomatoes, we used the least-squared mean virulence of each isolate across all wild and all domesticated tomato genotypes as two traits. We also calculated a domestication sensitivity trait; the relative difference in lesion size for each isolate between domesticated and wild hosts. Using these three traits, we conducted bigRR GWA within *B. cinerea* to map genes in the pathogen that respond to domestication shifts in the plant. Using the mean lesion area of the *B. cinerea* isolates on the wild or domesticated tomato hosts identified a complex, highly polygenic pattern of significant SNPs, similar to the individual tomato accessions (Figure 4, Figure 7). The significant SNP sets had a high degree of overlap between the wild phenotype and domesticated phenotype. In contrast, Domestication Sensitivity identified a more limited set of SNPs with less overlap to the mean lesion area on either Domesticated or Wild tomato (Figure 7). To query the underlying gene functions for these *B. cinerea* loci, we called genes as significant if there was one SNP within 2kb of the gene (Figure 7c). Using all 1251 genes linked to domestication traits by bigRR for a functional enrichment analysis found only 22 significantly overrepresented biological functions (Fisher exact test, p<0.05, Supplemental Data Set 2b) when compared to the whole-genome T4 gene annotation. The enrichments were largely surrounding enzyme and transport functions, which are known to be key components of how the pathogen produces toxic metabolites and conversely detoxifies plant defense compounds. Thus, there is an apparent subset of *B. cinerea* genes that may be specific to the genetic changes that occurred in tomato during domestication. Further work is needed to assess if and how variation in these genes may link to altered virulence on domesticated and wild tomatoes.

480

481

Discussion

The genetics of plant resistance to generalist pathogens are mostly quantitative, depend upon pathogen isolate, and rely on genetic variation in both signal perception and direct defense genes (Kover and Schaal 2002, Parlevliet 2002, Glazebrook 2005, Nomura, Melotto et al. 2005, Goss and Bergelson 2006, Tiffin and Moeller 2006, Rowe and Kliebenstein 2008, Barrett, Kniskern et al. 2009, Corwin, Copeland et al. 2016, Zhang, Corwin et al. 2017). Previous studies of tomato resistance to *B. cinerea* have found a quantitative genetic architecture that varies between domesticated and wild tomato species, with higher resistance in the wild species (Egashira, Kuwashima et al. 2000, Nicot, Moretti et al. 2002, Guimaraes, Chetelat et al. 2004, Finkers, van Heusden et al. 2007, Ten Have, van Berloo et al. 2007, Finkers, Bai et al. 2008). However, it was not known how the choice of *B. cinerea* isolate may change this plant-pathogen interaction. To address these questions, we used genetic variation in wild and domesticated tomato accessions in conjunction with a population of *B. cinerea* isolates. *B. cinerea* virulence on tomato, as measured by lesion size, was significantly affected by pathogen isolate, host genotype, and domestication status (Table 1). Pathogen isolate and tomato genotype were the strongest determinants of the interaction with only a slight but significant decrease in resistance to the pathogen associated with domestication. Equally, there was no evidence of a domestication bottleneck, with similar variance in resistance between the wild and domesticated tomato accessions (Table 1, Figure 2). There was also little evidence in this *B. cinerea* population for specialization to tomato, supporting the hypothesis that *B. cinerea* is a generalist at the isolate and species level (Figure 1 c-h) (Giraud, Fortini et al. 1999, Martinez, Blancard et al. 2003, Ma and Michailides 2005). GWA mapping within the pathogen showed that the genetics underlying *B. cinerea* virulence on tomato are highly quantitative and vary across tomato genotypes and domestication status (Figure 5, Figure 7). This analysis identified a small subset of pathogen genes whose variation contributes to differential virulence on most of the hosts tested, and a set of pathogen genes whose variation is responsive to tomato domestication (Supplemental Data Set 2 b).

Domestication and altered pathogen virulence genetics

513   In biotrophic pathogens, host domestication has decreased the diversity of

514 resistance alleles because they are lost in the domestication bottleneck as found for

515 specialist pathogens (Tanksley and McCouch 1997, Doebley, Gaut et al. 2006, Hyten,

516 Song et al. 2006, Chaudhary 2013). Surprisingly, we did not find evidence for a

517 domestication bottleneck in the phenotypic resistance to *B. cinerea* (Figure 2, Figure 3).

518 This is in contrast to genomic studies that explicitly show a genotypic bottleneck within

519 tomato domestication (Miller and Tanksley 1990, Koenig, Jiménez-Gómez et al. 2013).

520 Previous work in *A. thaliana* with these isolates has shown that if plant defenses such

521 as jasmonic acid and salicylic acid signaling are non-functional, there is increased

522 variation in *B. cinerea* virulence (Zhang, Corwin et al. 2017). Thus, if these pathways

523 had large effect differences between wild and domesticated tomato we would expect to

524 see a wider range of *B. cinerea* virulence phenotypes in domesticated tomato (Zhang,

525 Corwin et al. 2017). The similarity in the variance suggests that any differences we are

526 seeing are not caused by large effect changes that abolish or greatly diminish specific

527 defense signaling networks (Figure 2 and 3). These patterns, of mild decrease in

528 resistance to *B. cinerea* due to plant domestication, and within-species plant variation

529 exceeding the contribution of domestication itself, may be unique to interactions

530 between *B. cinerea* and tomato, or more general. It is unclear whether this pattern is

531 unique to tomato, or if each domestication event is unique.

532

533 **Polygenic quantitative virulence and breeding complications**

534   Our results indicate a highly polygenic basis of quantitative virulence of the

535 generalist *B. cinerea* on tomato similar to the highly polygenic basis on the host side of

536 the interaction (Zhang, Corwin et al. 2017).The variation in lesion size is linked to

537 numerous *B. cinerea* SNPs, each with small effect sizes (Figure 4a). Importantly, the

538 tomato host accession greatly influenced which *B. cinerea* loci were significantly

539 associated to lesion size (Figure 5). Thus, it possible that there is specialization at the

540 gene level, in which different alleles within the pathogen link to differential virulence on

541 specific host genotypes (Giraud, Fortini et al. 1999, Rowe and Kliebenstein 2007,

542 Blanco-Ulate, Morales-Cruz et al. 2014). This polygenic architecture of virulence is

543 different from virulence architecture in specialist pathogens that often have one or a few

544　large effect genes that control virulence (Keen 1992, De Feyter, Yang et al. 1993,

545　Abramovitch and Martin 2004, Boyd, Ridout et al. 2013, Vleeshouwers and Oliver

546　2014). Further studies are needed to compare how the host plant species may affect

547　this image of genetic variation in virulence.

548　　　　These results indicate particular challenges for breeding durable resistance to *B.*

549　*cinerea*, and possibly other generalist pathogens. The highly polygenic variation in

550　virulence, combined with genomic sequencing showing that this pathogen is an inter-

551　breeding population, suggests that the pathogen is actively blending a large collection of

552　polymorphic virulence loci (Rowe and Kliebenstein 2007, Fekete, Fekete et al. 2012,

553　Atwell, Corwin et al. 2015, Atwell, Corwin et al. 2018). Thus, it is insufficient to breed

554　crop resistance against a single isolate of *B. cinerea*, as this resistance mechanism

555　would likely be rapidly overcome by new genotypes within the field population of *B.*

556　*cinerea*. In contrast, it is likely necessary to breed resistance using a population of the

557　pathogen, and to focus on plant loci that target entire virulence pathways or

558　mechanisms. The results in this study indicate that the specific genetics of the plant

559　host, the host's general domestication status, and the specific genetics of the pathogen

560　isolate will all combine to affect how the estimated breeding value inferred from any

561　experiment will translate to a field application (Table 1). As such, utilizing a single or

562　even a few pathogen isolates to guide resistance breeding in plants is unlikely to

563　translate to durable resistance against *B. cinerea* as a species. Further, the lack of

564　evidence for a domestication bottleneck on tomato resistance to B*. cinerea* suggests

565　that, at least for tomato, allelic variation in this generalist pathogen is sufficient to

566　overcome introgression of wild resistance genes or alleles into the domesticated crop.

567　　　　This study examined the contributions of host and pathogen natural genetic

568　variation to the quantitative interaction in the tomato-*B. cinerea* pathosystem. *B. cinerea*

569　has a highly quantitative genetic basis of virulence on tomato, which is dominated by

570　pathogen effects but also sensitive to genetic variation linked to tomato domestication.

571　Future studies are necessary to test if this pattern of domestication responses in tomato

572　is similar to patterns in other crops. Because this population of *B. cinerea* can infect a

573　wide range of hosts, it will be possible to directly conduct this study. By extending future

574　work to additional domestication events, it may be possible to test whether independent

575   crop domestication events have a consistent underlying genetic signal of *B. cinerea*

576   adaptation to plant domestication.

577

578

Methods

Tomato genetic resources

We obtained seeds for 12 selected tomato genotypes in consultation with the UC Davis Tomato Genetics Resource Center. These include a diverse sample of 6 genotypes of domesticated tomato's closest wild relative (*S. pimpinellifolium*) sampling across its major geographic regions (Peru, Ecuador) and 6 heritage and modern varieties of *S. lycopersicum*, focusing on mid- to late-20th century improved varieties (Lin, Zhu et al. 2014, Blanca, Montero-Pau et al. 2015). While genetic data is not available for all of our *S. pimpinellifolium* accessions, 9 of the 12 accessions have been genotyped and span the mappable diversity in domesticated tomato and its close relatives (Sim, Durstewitz et al. 2012) (Supplemental Figure 2). We bulked all genotypes in long-day (16h photoperiod) greenhouse conditions at UC Davis in fall 2014. We grew plants under metal-halide lamps using day/night temperatures at 25°C/18°C in 4" pots filled with standard potting soil (Sunshine mix #1, Sun Gro Horticulture). Plants were watered once daily and pruned and staked to maintain upright growth. Fruits were collected at maturity and stored at 4°C in dry paper bags until seed cleaning. To clean the seeds, we incubated seeds and locule contents at 24°C in 1% protease solution (Rapidase C80 Max) for 2h, then rinsed them in deionized water and air-dried. We then stored seeds in a cool, dry, dark location until use.

To grow plants for detached leaf assays, we bleach-sterilized all seeds and germinated them on paper in the growth chamber using flats covered with humidity domes. At 7 days we transferred seedlings to soil (SunGro Horticulture, Agawam, MA) and grew all plants in growth chambers in 20°C, short-day (10h photoperiod) conditions with 180-190 uM light intensity and 60% RH. We bottom-watered with deionized water every two days for two weeks, and at week 3 watered every two days with added nutrient solution (0.5% N-P-K fertilizer in a 2-1- 2 ratio; Grow More 4-18-38). The plants were used for detached leaf assays 6 weeks after transferring seedlings to soil. Flowering in this system did not occur until minimally 9 weeks of age for any accession, and as such we were sampling midway between the juvenile/adult transition and any flowering time decision. This window has been successful to minimize any major

609 ontogenetic effects on the pathogen/host interaction in other systems (Corwin,

610 Copeland et al. 2016).

611

612 ***B. cinerea* genetic resources**

613   We utilized a previously described collection of *B. cinerea* isolates that were

614 isolated as single spores from natural infections of fruit and vegetable tissues collected

615 in California and internationally (Atwell, Corwin et al. 2015, Zhang, Corwin et al. 2017, Atwell,

616 Corwin et al. 2018). This included five isolates obtained from natural infections of tomato.

617 We maintained *B. cinerea* isolates as conidial suspensions in 30% glycerol for long-term

618 storage at -80°C. For regrowth, we diluted spore solutions to 10% concentration in filter-

619 sterilized 50% grape juice, and then inoculated onto 39g/L potato dextrose agar (PDA)

620 media. We grew isolates at 25°C in 12h light and propagated every 2 weeks.

621 Sequencing failed for 6 out of our 97 phenotyped isolates. For bigRR GWA mapping

622 with the 91 isolates genotyped in this study, we utilized a total of 272,672 SNPs against

623 the *B. cinerea* T4 genome with minor allele frequency (MAF) 0.20 or greater, and less

624 than 10% missing calls across the isolates (SNP calls in at least 82/ 91 isolates) (Atwell,

625 Corwin et al. 2018).

626

627 **Detached leaf assay**

628   To study the effect of genetic variation in host and pathogen on lesion formation,

629 we infected detached leaves of 12 diverse tomato varieties with the above 97 *B. cinerea*

630 isolates. We used a randomized complete block design for a total of 6 replicates across

631 2 experiments. In each experiment, this included a total of 10 plants per genotype

632 randomized in 12 flats in 3 growth chambers. Each growth chamber block corresponded

633 with a replicate of the detached leaf assay, such that growth chamber and replicate

634 shared the same environmental block. At 6 weeks of age, we selected 5 leaves per

635 plant (expanded leaves from second true leaf or younger), and 2 leaflet pairs per leaf.

636 We randomized the order of leaves from each plant, and the leaflets were placed on 1%

637 phytoagar in planting flats, with humidity domes. Our inoculation protocol followed

638 previously described methods (Denby, Kumar et al. 2004, Kliebenstein, Rowe et al.

639 2005). Spores were collected from mature *B. cinerea* cultures grown on canned peach

640   plates and diluted to 10 spores/ μL in filter-sterilized 50% organic grape juice. Spores in

641   grape juice were maintained in 4°C refrigeration or on ice from the time of collection, to

642   inhibit germination prior to inoculation. The diluted spore suspensions were

643   homogenized by agitation continuously during the entire process of applying the spores

644   to all samples. This maintains the spores in the suspension and ensures even

645   application across samples, then 4μl droplets were placed onto the detached leaflets at

646   room temperature. The entire inoculation took approximately 2 hours of time per

647   experiment. Mock-inoculated control leaves were treated with 4μL of 50% organic grape

648   juice without spores. Digital photos were taken of all leaflets at 24, 48, and 72 hours

649   post inoculation and automated image analysis was used to measure lesion size.

650

651   **Automated Image Analysis**

652   Lesion area was digitally measured using the EBImage and CRImage packages

653   (Pau, Fuchs et al. 2010, Failmezger, Yuan et al. 2012) in the R statistical environment

654   (R Development Core Team 2008), as previously described (Corwin, Copeland et al.

655   2016, Corwin, Subedy et al. 2016). Leaflets were identified as objects with green hue,

656   and lesions were identified as low-saturation objects within leaves. Images masks were

657   generated for both the leaf and lesion, then manually refined by a technician to ensure

658   accurate object calling. The area of these leaves and lesions were then automatically

659   measured as pixels per lesion and converted to area using a 1 cm reference within each

660   image.

661

662   **Data analysis**

663   We analyzed lesion areas using general linear models for the full experiment to

664   determine the contributions of plant and pathogen genotype(R lme4 package; (Bates,

665   Maechler et al. 2015))Two of our 97 isolates that did not have replication across 2

666   experiments were dropped at this stage of analysis. We used the following linear

667   models throughout our analyses.

668   Main mixed-effect model of lesion size variation

669    $Y = I + D/P + I{:}D + I{:}D/P + W_R/L/A + E_R + E_R{:}I$

670   Within-plant accession mixed-effect model of lesion size

671    $Y = I + W_R/L/A + E_R + E_R{:}I$

672 Within-isolate mixed-effect model of lesion size
673 $Y = D/P + E_R$
674
675   Where I represents fungal genotype (isolate), P represents plant genotype

676 (accession), D represents domestication status, E represents experiment, W represents

677 whole plant, L represents leaf, A represents leaflet position. Factors with the subscript R

678 are included in the analysis as random effects.

679   The within-plant accession model was used to calculate the significance of each

680 factor and to obtain the least-squared means of lesion size for each *B. cinerea* isolate x

681 tomato accession as well as for each *B. cinerea* isolate x domesticated/ wild tomato. We

682 also calculated a domestication sensitivity phenotype, Sensitivity = (Domesticated lesion

683 size – Wild lesion size) / Domesticated lesion size.

684   We bootstrapped assignment of plant accessions to domestication groups in

685 order to assess the robustness of our observed domestication effects. We randomly

686 drew three genotypes from the domesticated and wild groupings and assigned them to

687 a new pseudo-wild grouping. The other six genotypes were assigned as a pseudo-

688 domesticated grouping and the model was rerun. This bootstrapping was repeated 100

689 times with each representing a random draw. We used these to repeat the full model

690 and to repeat the individual isolate models, as a test of the robustness of the tomato

691 domestication effect.

692   Using tomato sequence data from the SolCAP diversity panel that contained 9 of

693 our 12 accessions, we determined pairwise genetic distances between our accessions

694 (Sim, Durstewitz et al. 2012). We calculated pairwise Euclidean distances between 426

695 wild and domesticated tomato accessions from Infinium SNP genotyping at 7,720 loci

696 using the R adegenet package (Jombart , Sim, Durstewitz et al. 2012). Clustering is by

697 R hclust (in the stats package) default UPGMA method (R Development Core Team

698 2008).

699   We used several methods to examine host specialization to tomato within *B.*

700 *cinerea*. First, we split our *B. cinerea* population into isolates collected from tomato

701 tissue vs. other hosts. We compared these groups by t-test for virulence on

702 domesticated tomato genotypes, wild tomato genotypes, or all tomato genotypes. Next,

703 we used a Wilcoxon signed-rank test to compare the rank order distribution of model-

704   adjusted lesion sizes across paired tomato genotypes. Also, to examine host

705   specialization to tomato domestication within *B. cinerea*, we used a Wilcoxon signed-

706   rank test to compare the rank order of model-adjusted lesion sizes across all

707   domesticated vs. all wild tomato genotypes. Finally, we conducted single-isolate

708   ANOVAs with FDR correction on general linear models to identify isolates with a

709   significant response to plant genotype or domestication status.

710   The model means and Domestication Sensitivity were used as the phenotypic

711   input for GWA using bigRR, a heteroskedastic ridge regression method that

712   incorporates SNP-specific shrinkage (Shen, Alam et al. 2013). This approach has

713   previously had a high validation rate (Ober, Huang et al. 2015, Corwin, Copeland et al.

714   2016, Francisco, Joseph et al. 2016, Kooke, Kruijer et al. 2016). The *B. cinerea* bigRR

715   GWA used 272,672 SNPs at MAF 0.20 or greater and <10% missing SNP calls as

716   described above (Atwell, Corwin et al. 2018). Because bigRR provides an estimated

717   effect size, but not a p-value, significance was estimated using 1000 permutations to

718   determine effect significance at 95%, 99%, and (approximately) 99.9% thresholds

719   (Doerge and Churchill 1996, Shen, Alam et al. 2013, Corwin, Copeland et al. 2016).

720   SNPs were annotated by custom R scripts with gene transfer format file construction

721   from the T4 gene models for genomic DNA by linking the SNP to genes within a 2kbp

722   window (http://www.broadinstitute.org, (Staats and van Kan 2012)). Functional

723   annotations are based on the T4 gene models for genomic DNA

724   (http://www.broadinstitute.org, *B. cinerea*; (Staats and van Kan 2012)). Additional genes

725   of interest, based on a broad literature search of known virulence loci, were taken from

726   NCBI (https://www.ncbi.nlm.nih.gov/) and included by mapping sequence to the T4

727   reference using MUMmer v3.0 (Kurtz, Phillippy et al. 2004).

728   To predict expected overlap of significant SNPs across plant genotypes, we used

729   the average number of significant SNPs per each of the 12 plant genotypes (14,000

730   SNPs) and calculated expected overlap between those 12 lists using binomial

731   coefficients. Functional annotations of the gene lists are based on the T4 gene models

732   for genomic DNA (http://www.broadinstitute.org, *B. cinerea*; (Staats and van Kan 2012).

733

734   **Supplemental Data Files**

747

748

749 **Figure Legends**

750

751 **Figure 1. *Botrytis cinerea* x tomato diversity in detached leaf assay and digital**

752 **image analysis.** a) Individual tomato leaflets of 6 *S. lycopersicum* genotypes and 6 *S.*

753 *pimpinellifolium* genotypes are in randomized rows, spore droplets of individual *B.*

754 *cinerea* isolates are in randomized columns. Digital images are collected 72 hours post

755 inoculation. Single droplets of 40 *B. cinerea* spores are infected on randomized leaflets

756 using randomized isolates, and digital images are taken 72 hours post inoculation.

757 b) Digital masking of leaf and lesion is followed by automated measurement of area for

758 each lesion.

759 c-h) Variation in lesion size resulting of the interaction of *B. cinerea* and diverse tomato

760 genotypes.

761 c) Average lesion size of single *B. cinerea* isolates (line traces) across tomato host

762 genotypes grouped by domestication status.

763 d) Highlight of the common reference *B. cinerea* isolate B05.10.

764 e) Highlight of the ten highest-virulence isolates, as estimated by mean virulence across

765 all tomato genotypes.

766 f) Highlight of the ten most saprophytic, or low virulence, isolates, as estimated by mean

767 virulence across all genotypes.

768 g) Highlight of the five isolates collected from tomato tissue.

769 h) Highlight of the two isolates with significant domestication sensitivity.

770

771 **Figure 2. Distribution of tomato genotype susceptibility to infection with 97**

772 **genetically diverse *B. cinerea* isolates.**

773 Violin plots show the distribution of lesion size caused by B. cinerea isolates on each

774 tomato host genotype. Individual points are mean lesion size for each of the 97 different

775 isolate-host pairs. The boxes show the 75th percentile distribution, and the horizontal
776 line shows the mean resistance of the specific host genotype. The tomato genotypes
777 are grouped based on their status as wild or domesticated germplasm.
778
779 **Figure 3. Distribution of *B. cinerea* virulence by tomato domestication status.**
780 The violin plots show the mean virulence of each *B. cinerea* isolate on the tomato
781 genotypes, grouped as wild or domesticated germplasm. The domestication effect on
782 lesion size is significant (Table 1 ANOVA, p=0.0006). The interaction plot between the
783 two violin plots connects the average lesion size of a single *B. cinerea* isolate between
784 the wild and domesticated germplasm.
785
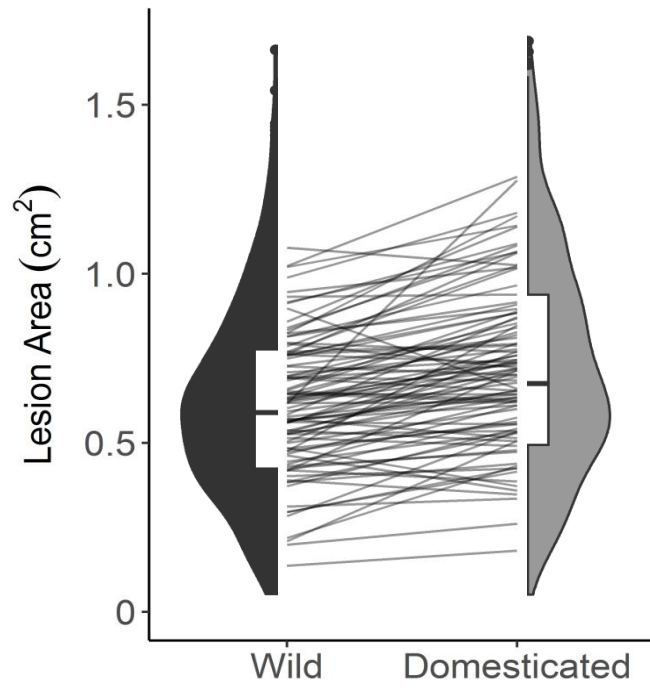786 **Figure 4. GWA of *B. cinerea* lesion size on individual tomato genotypes.**
787 Botrytis cinerea chromosomes are differentiated by shading, alternating light and dark
788 grey.
789 a) Manhattan plot of estimated SNP effect sizes from bigRR for *B. cinerea* lesion size
790 using a single tomato accession, LA2093. Permutation-derived thresholds are shown in
791 horizontal dashed lines.
792 b) The number of tomato accessions for which a *B. cinerea* SNP was significantly linked
793 to lesion development by bigRR using the 99% permutation threshold. Frequency is
794 number of phenotypes in which the SNP exceeds the threshold. Vertical dotted lines
795 identify regions with overlap between the top 100 large-effect SNPs for LA2093 and
796 significance across the majority (≥6) of tomato genotypes tested.
797
798 **Figure 5. Frequency of overlap in *B. cinerea* GWA significance across tomato**
799 **accessions.**
800 a) The frequency with which the *B. cinerea* SNPs significantly associate with lesion size
801 on the 12 tomato accessions using bigRR and the 99% permutation threshold. The
802 black line indicates the expected frequency of random overlap, given the number of
803 significant SNPs per plant genotype and size of total SNP set. The inset zooms in on
804 the distribution for overlapping SNPs above 6 plant genotypes for easier visualization.
805 There were no SNPs expected to overlap by random chance in the inset.
806 b) The frequency with which *B. cinerea* genes significantly associated with lesion size
807 on the 12 tomato accessions. Genes were called as significant if there was one
808 significant SNP called at the 99% permutation threshold within the gene body, or within
809 2kb of the gene body.
810
811 **Figure 6. Host specificity of significant SNPs linked to the gene BcT4_6001**
812 **(Bcin14g00870).**
813 a) SNPs with effects estimates above the 99% permutation threshold are colored by
814 trait (plant accession in which the effect was estimated). Wild accessions are oranges
815 (yellow to red shades) and domesticated accessions are blues (green to purple
816 shades). BcT4_6001 (Bcin14g00870) is a pectinesterase gene linked to at least one
817 significant SNP on all 12 of the tested tomato accessions by bigRR. The annotated
818 exons are depicted as turquoise rectangles, with the start codon marked with an arrow
819 indicating the direction of transcription. Red rectangles indicate corresponding linkage
820 disequilibrium blocks from Figure 6b.

821   b) Linkage disequilibrium plot, including all pairwise comparisons of SNPs in the 2kb
822   region surrounding Bcin14g00870. The color scheme for each SNP pair is D'/LOD:
823   white if LOD <2 and D' <1, bright red for LOD ≥2 and D'=1, intermediate shades for
824   LOD≥2 and D'<1. The number within each square represents the D' value for each
825   pairwise comparison if <1.
826
827   **Figure 7. GWA analysis of domestication sensitivity in *B. cinerea.***
828   Domestication sensitivity of each isolate was estimated as the difference between the
829   average virulence on the wild and domesticated tomato germplasm. This was then
830   utilized for GWA mapping by bigRR.
831   a) The top 1000 SNPs that significantly affect lesion size across domesticated tomato,
832   wild tomato or domestication sensitivity are shown. Significance is called as crossing
833   the 99% permutation threshold.
834   b) Venn diagram of overlapping SNPs identified as crossing the 99% permutation
835   threshold for each trait.
836   c) Venn diagram of overlapping genes identified as crossing the 99% permutation
837   threshold for each trait. Genes were called as significant if there was one significant
838   SNP within the gene body or within 2kb of the gene body.
839
840
841   Acknowledgements
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846

Figure 1. *Botrytis cinerea* x tomato diversity in detached leaf assay and digital image analysis. a) Individual tomato leaflets of 6 *S. lycopersicum* genotypes and 6 *S. pimpinellifolium* genotypes are in randomized rows, spore droplets of individual *B. cinerea* isolates are in randomized columns. Digital images are collected 72 hours post inoculation. Single droplets of 40 *B. cinerea* spores are infected on randomized leaflets using randomized isolates, and digital images are taken 72 hours post inoculation.

b) Digital masking of leaf and lesion is followed by automated measurement of area for each lesion.

c-h) Variation in lesion size resulting of the interaction of *B. cinerea* and diverse tomato genotypes.

c) Average lesion size of single *B. cinerea* isolates (line traces) across tomato host genotypes grouped by domestication status.

d) Highlight of the common reference *B. cinerea* isolate B05.10.

e) Highlight of the ten highest-virulence isolates, as estimated by mean virulence across all tomato genotypes.

f) Highlight of the ten most saprophytic, or low virulence, isolates, as estimated by mean virulence across all genotypes.

g) Highlight of the five isolates collected from tomato tissue.

h) Highlight of the two isolates with significant domestication sensitivity.
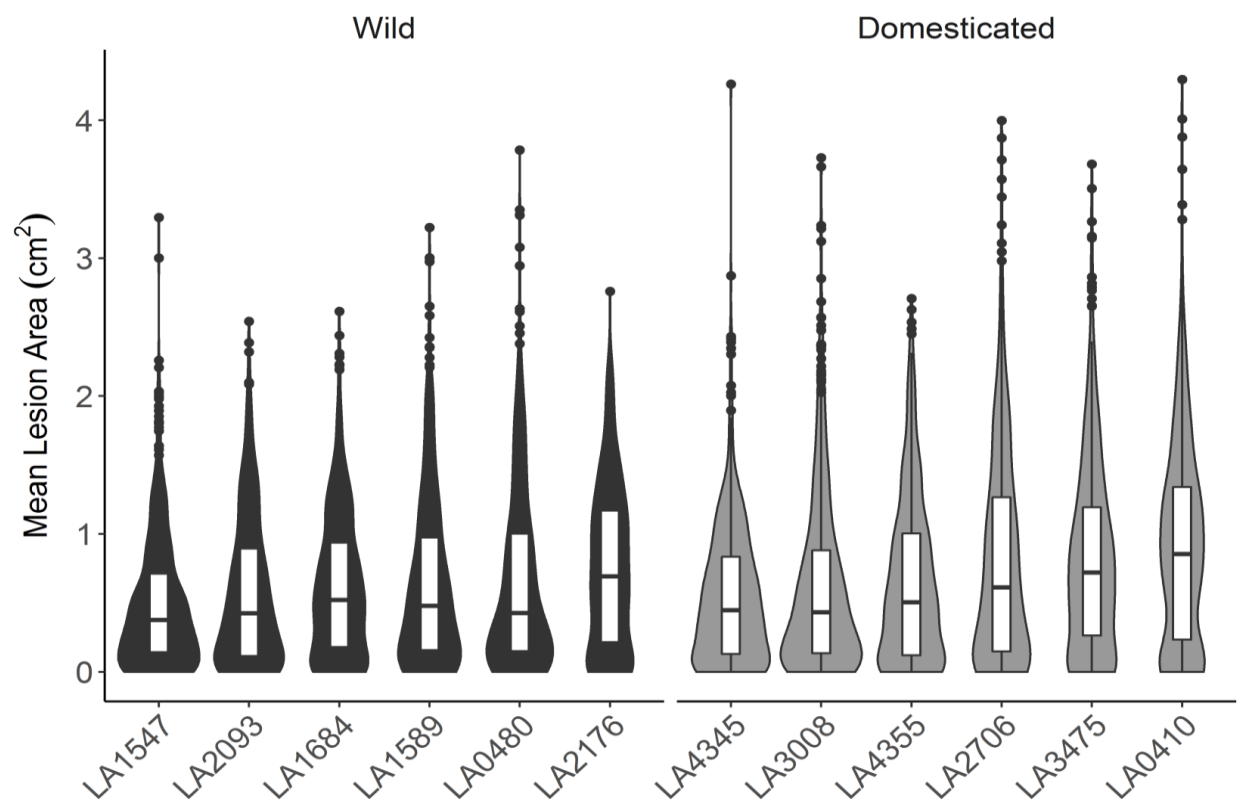
Figure 2. Distribution of tomato genotype susceptibility to infection with 97 genetically diverse *B. cinerea* isolates.

Violin plots show the distribution of lesion size caused by *B. cinerea* isolates on each tomato host genotype. Individual points are mean lesion size for each of the 97 different isolate-host pairs. The boxes show the 75th percentile distribution, and the horizontal line shows the mean resistance of the specific host genotype. The tomato genotypes are grouped based on their status as wild or domesticated germplasm.

Figure 3. Distribution of *B. cinerea* virulence by tomato domestication status.

The violin plots show the mean virulence of each *B. cinerea* isolate on the tomato genotypes, grouped as wild or domesticated germplasm. The domestication effect on lesion size is significant (Table 1 ANOVA, p=0.0006). The interaction plot between the two violin plots connects the average lesion size of a single *B. cinerea* isolate between the wild and domesticated germplasm.

a

Lesion Size on LA2093

95% Threshold
99% Threshold

Estimated Effect Size (mm^2)

Chromosome

b

Plant Genotypes per Significant SNP
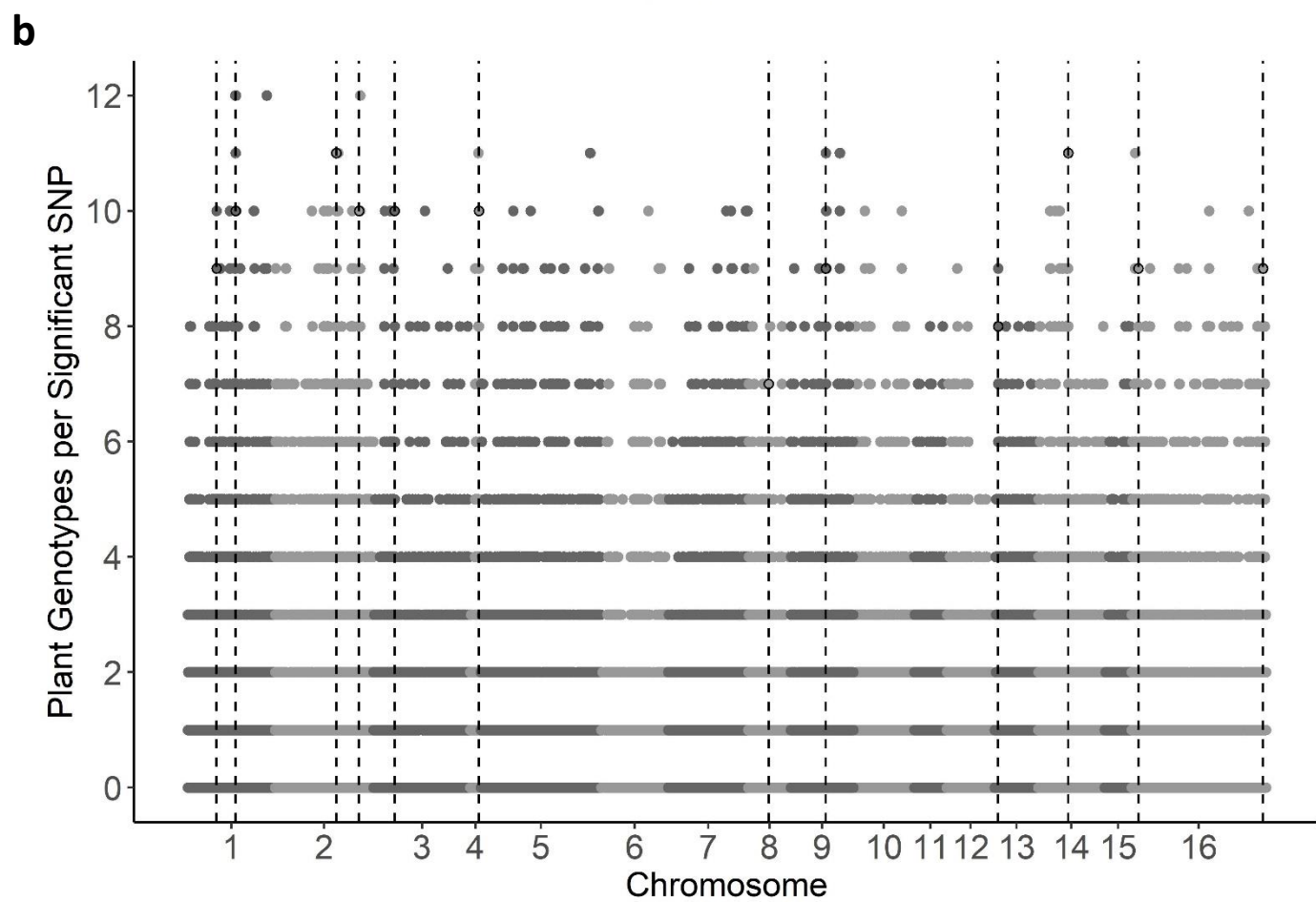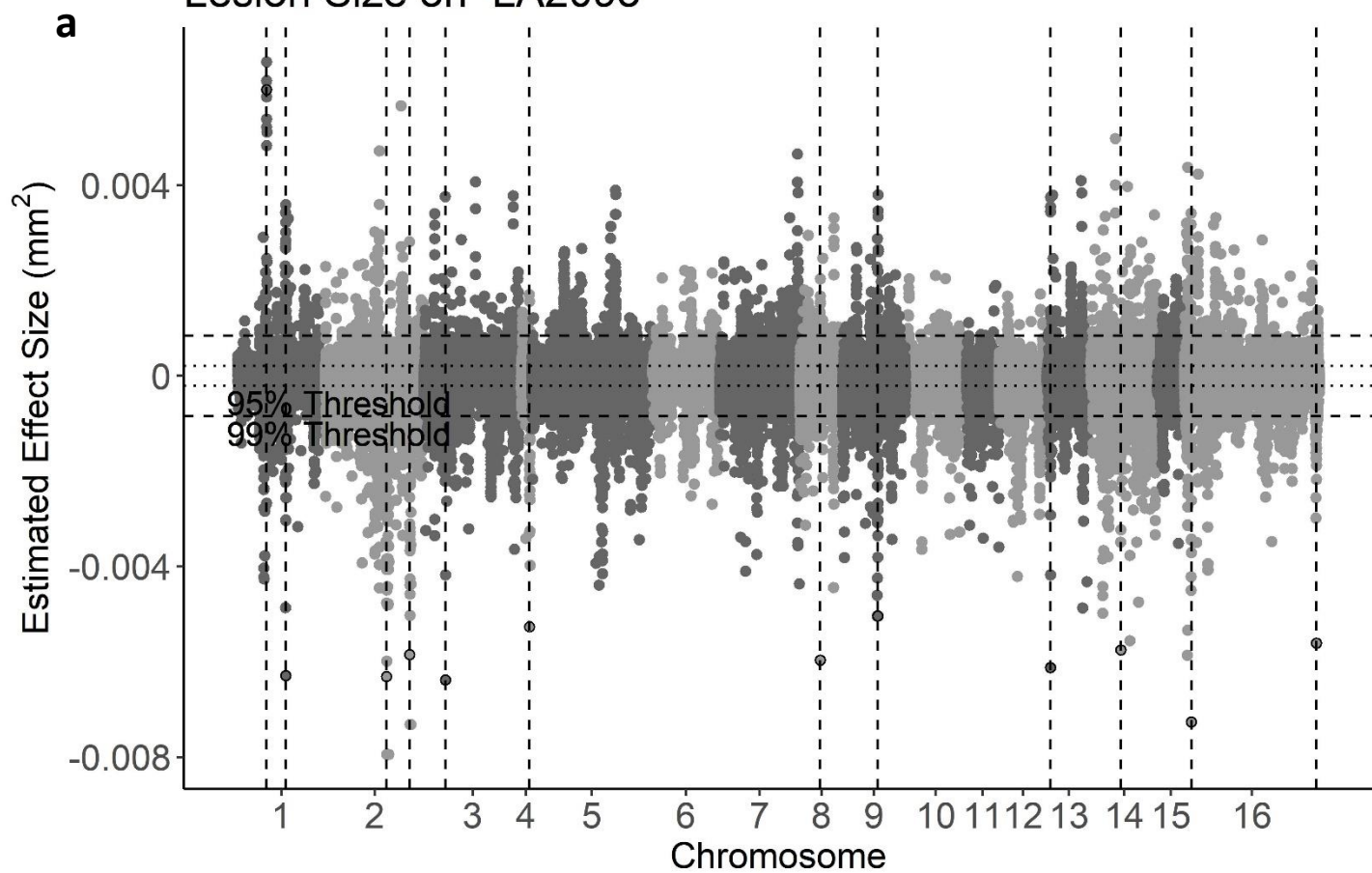
Chromosome

Figure 4. GWA of *B. cinerea* lesion size on individual tomato genotypes.

Botrytis cinerea chromosomes are differentiated by shading, alternating light and dark grey.

a) Manhattan plot of estimated SNP effect sizes from bigRR for *B. cinerea* lesion size using a single tomato accession, LA2093. Permutation-derived thresholds are shown in horizontal dashed lines.

b) The number of tomato accessions for which a *B. cinerea* SNP was significantly linked to lesion development by bigRR using the 99% permutation threshold. Frequency is number of phenotypes in which the SNP exceeds the threshold. Vertical dotted lines identify regions with overlap between the top 100 large-effect SNPs for LA2093 and significance across the majority (≥6) of tomato genotypes tested.
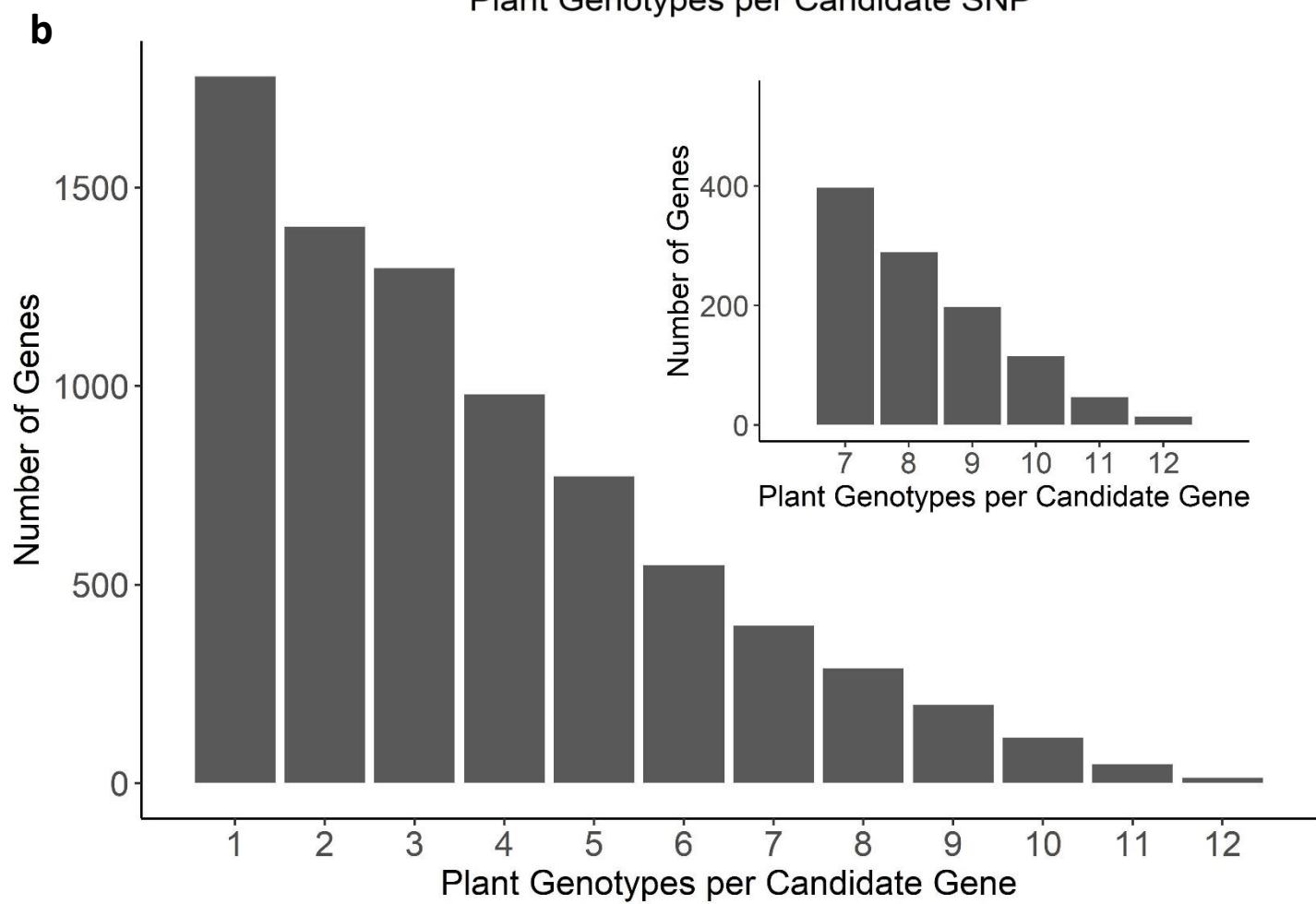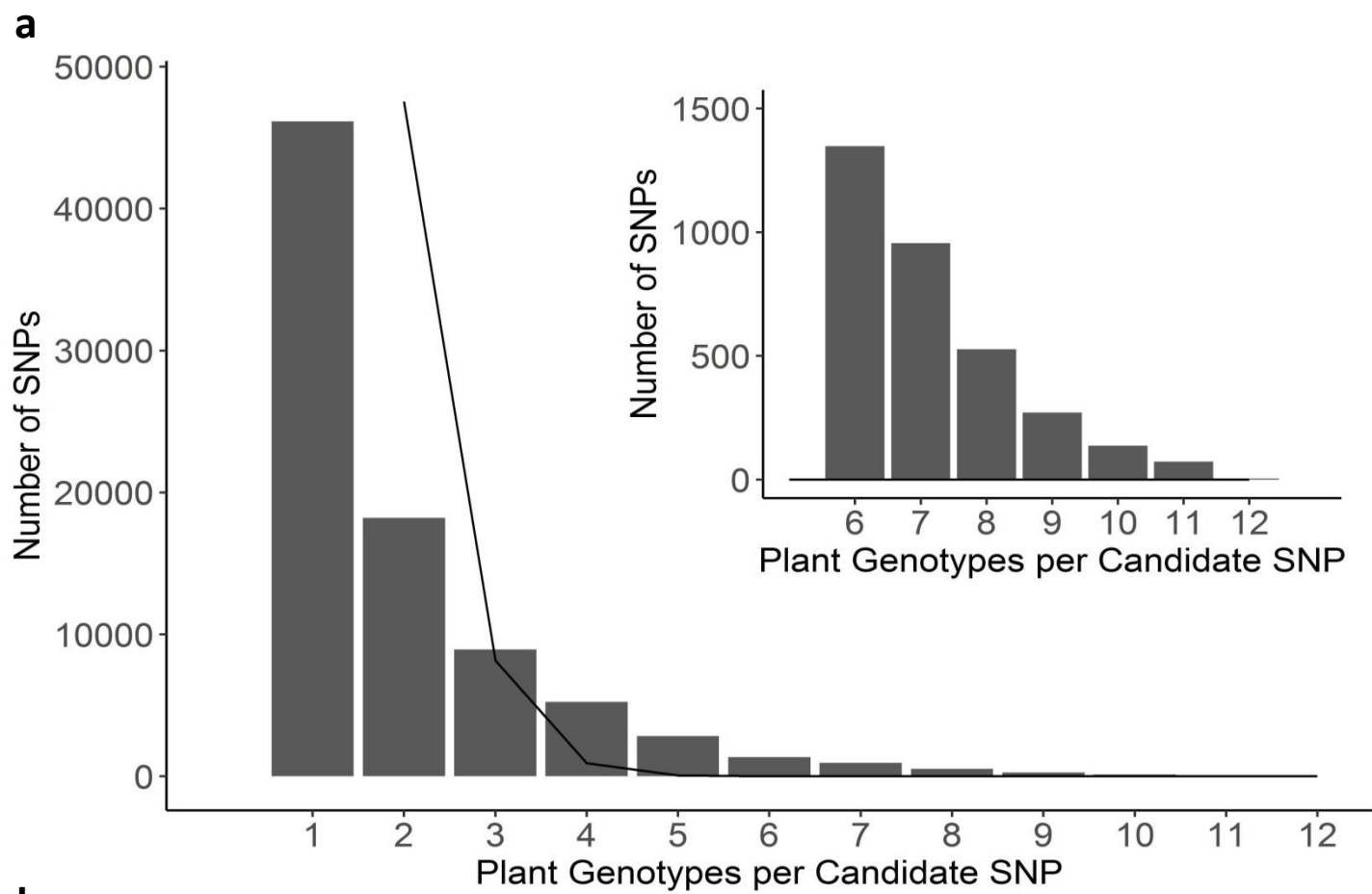
Figure 5. Frequency of overlap in *B. cinerea* GWA significance across tomato accessions.

a) The frequency with which the *B. cinerea* SNPs significantly associate with lesion size on the 12 tomato accessions using bigRR and the 99% permutation threshold. The black line indicates the expected frequency of random overlap, given the number of significant SNPs per plant genotype and size of total SNP set. The inset zooms in on the distribution for overlapping SNPs above 6 plant genotypes for easier visualization. There were no SNPs expected to overlap by random chance in the inset.

b) The frequency with which *B. cinerea* genes significantly associated with lesion size on the 12 tomato accessions. Genes were called as significant if there was one significant SNP called at the 99% permutation threshold within the gene body, or within 2kb of the gene body.
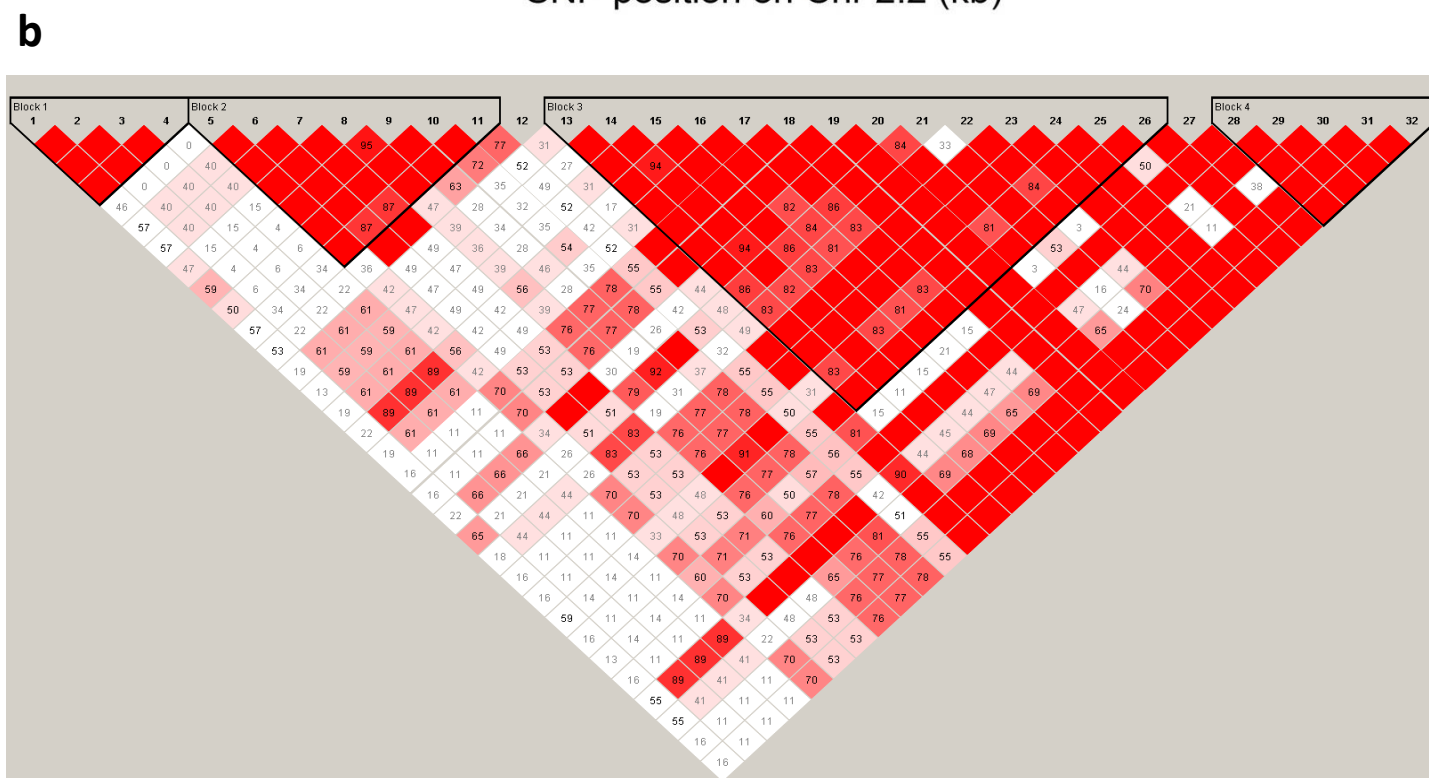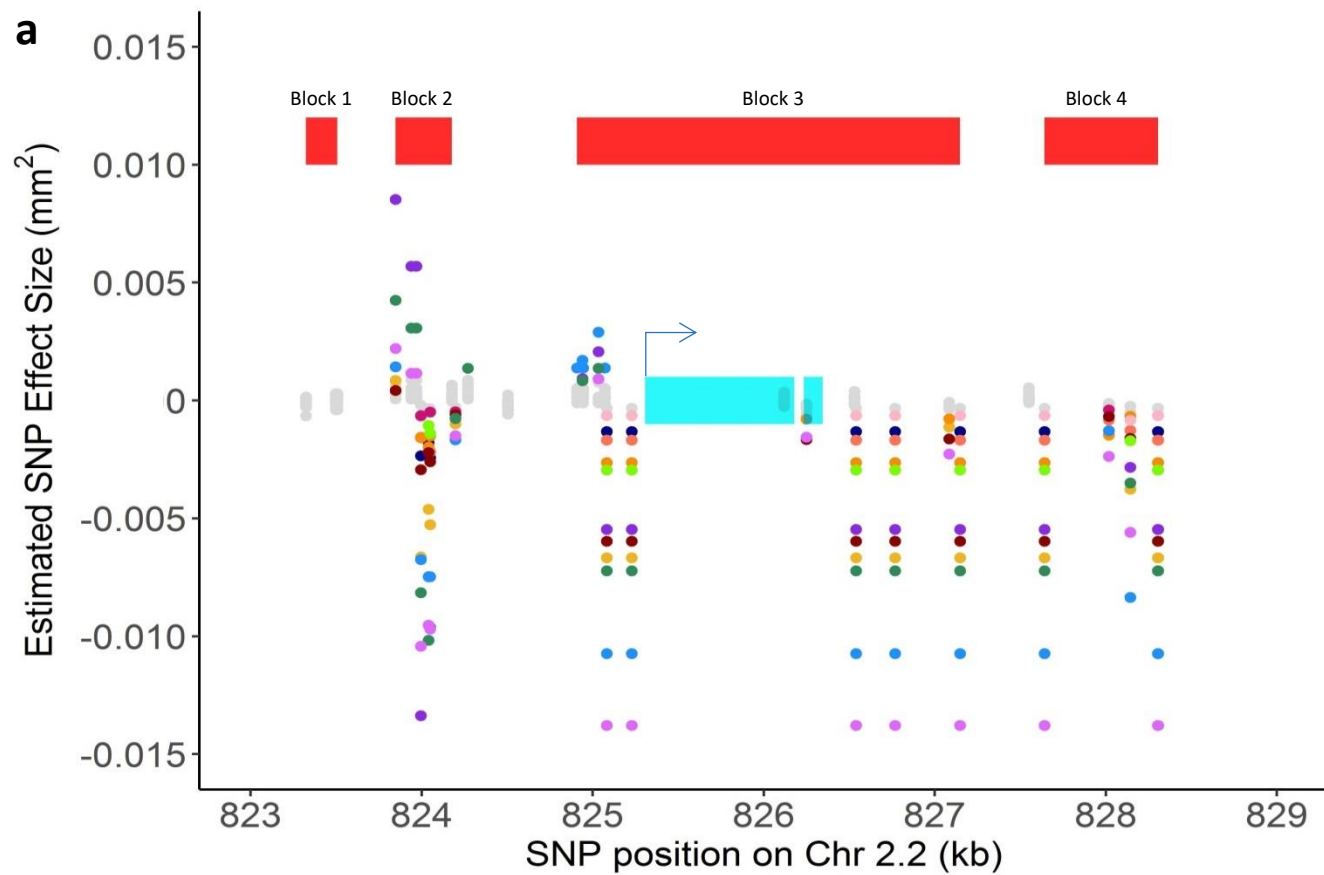
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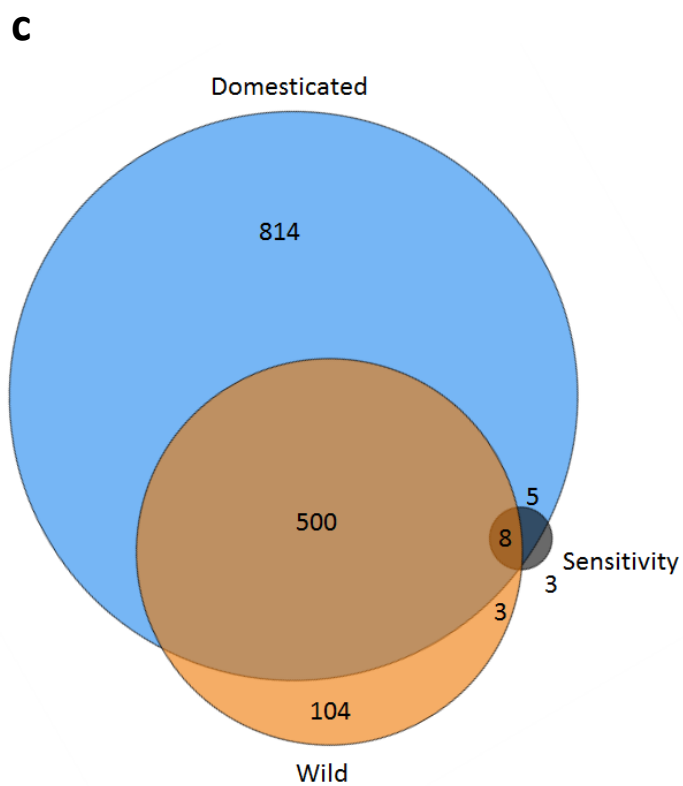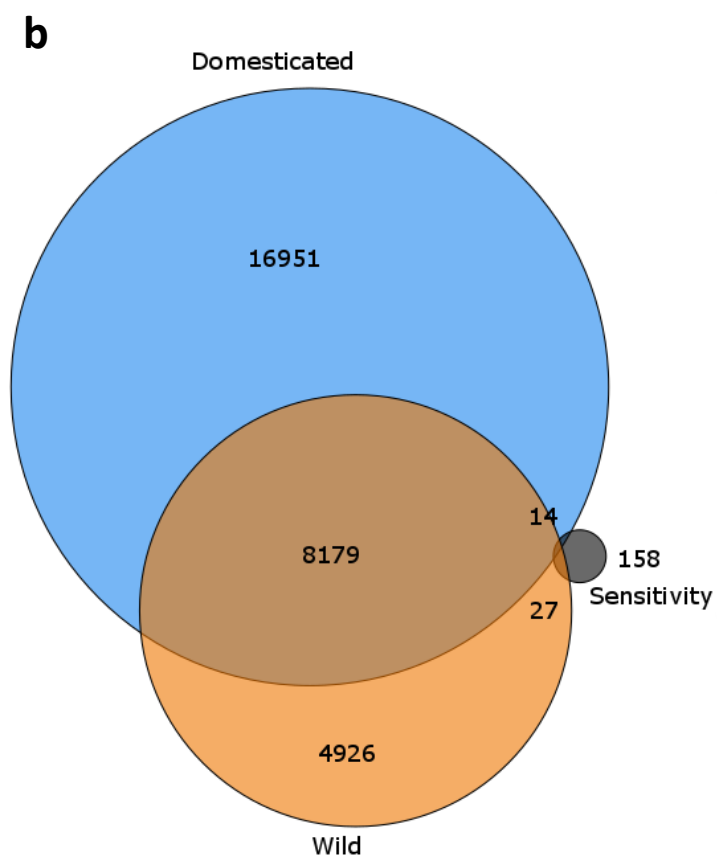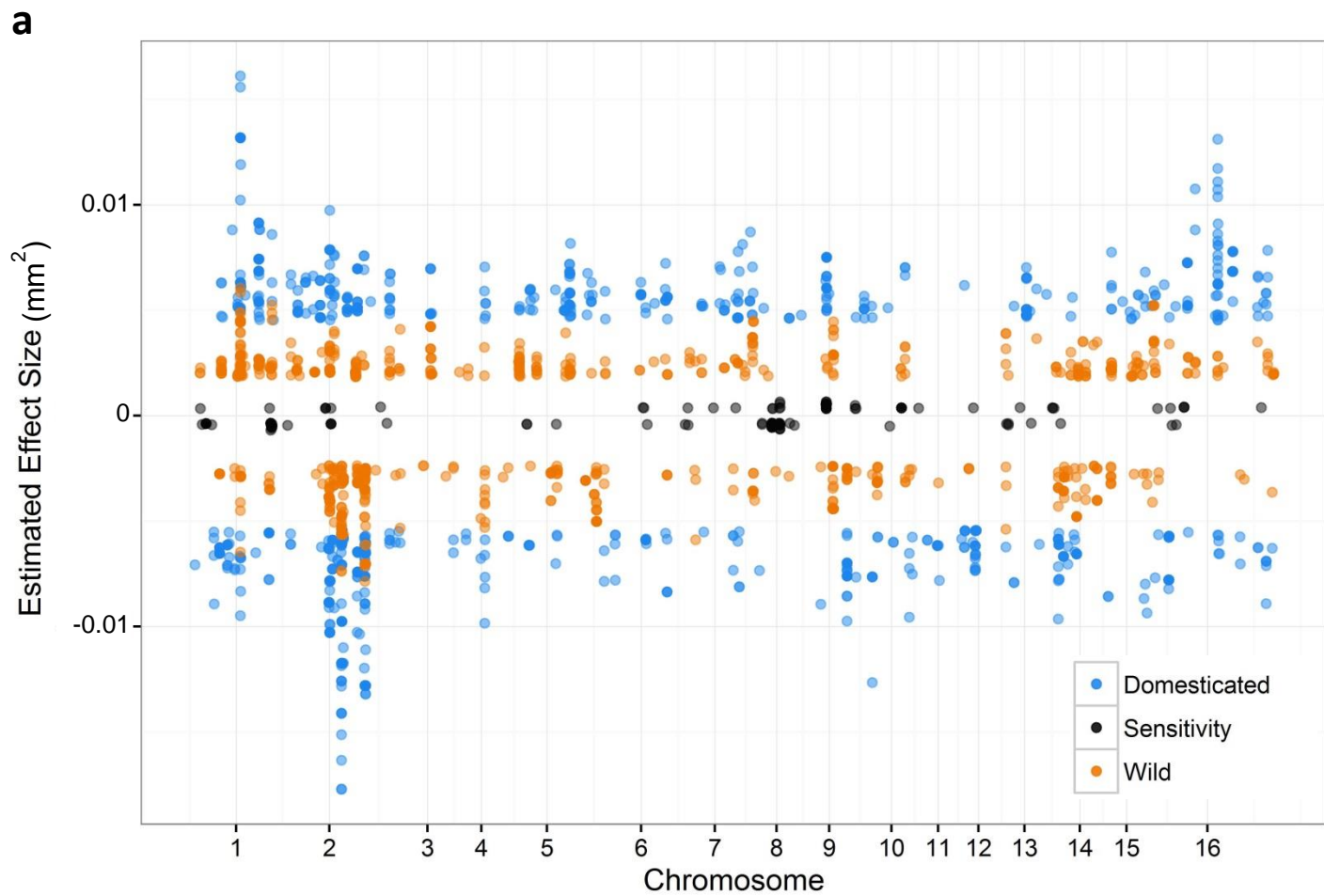
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