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12   **Title: Crop domestication and pathogen virulence: Interactions of tomato and  
13   *Botrytis* genetic diversity**

14

15   Short title: Interactions of tomato and *Botrytis* genetics

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21       **Abstract**

22           Human selection during crop domestication alters numerous traits, including  
23 disease resistance. Little is known about how crop domestication affects quantitative  
24 interactions with generalist pathogens. To study how crop domestication impacts plant  
25 resistance to generalist pathogens, and correspondingly how this interacts with the  
26 pathogen's genetics, we infected a collection of wild and domesticated tomato  
27 accessions with a genetically diverse population of the generalist pathogen *Botrytis*  
28 *cinerea*. We quantified variation in lesion size of 97 *B. cinerea* genotypes (isolates) on 6  
29 domesticated *Solanum lycopersicum* and 6 wild *S. pimpinellifolium* genotypes. Lesion  
30 size was significantly controlled by plant domestication, plant genetic variation, and the  
31 pathogen's genotype. Overall, resistance was slightly elevated in the wild tomato  
32 accessions. Genome-wide association (GWA) mapping in *B. cinerea* identified a highly  
33 polygenic collection of genes. This suggests that breeding against this pathogen would  
34 need to utilize a diversity of isolates to capture all possible mechanisms. Critically, we  
35 identified a discrete subset of *B. cinerea* genes where the allelic variation was linked to  
36 altered virulence against the wild versus domesticated tomato accessions. This  
37 indicates that this generalist pathogen already has the necessary allelic variation in  
38 place to handle the introgression of wild resistance mechanisms into the domesticated  
39 crop.

40

41       **Introduction**

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

52 pathogen (Dangl and Jones 2001, Jones and Dangl 2006, Dodds and Rathjen 2010,  
53 Pieterse, Van der Does et al. 2012). These recognition signals can be conserved  
54 pathogen patterns such as cell-wall polymers or flagellin, or alternatively, specific  
55 virulence factors that block perception of the pathogen, and in turn are detected by plant  
56 proteins that guard the signaling networks (Jones and Dangl 2006, Bittel and Robatzek  
57 2007, Ferrari, Galletti et al. 2007, Boller and He 2009, Dodds and Rathjen 2010). The  
58 evolution of large-effect qualitative loci has partly been driven by the narrow host range  
59 for the pathogen that enhances co-evolution between host resistance genes and  
60 pathogen virulence mechanisms.

61 In contrast to specialist pathogens, generalist pathogens are virulent across a  
62 wide range of plant host species. Generalist pathogens potentially have less stringent  
63 co-evolution to specific hosts and their accompanying resistance mechanisms, because  
64 these pathogens can easily shift to new hosts in the environment. This allows generalist  
65 pathogens to evade the rapid evolution of new resistance mechanisms within specific  
66 hosts until they evolve to counter this new resistance. This niche-shifting ability may  
67 partially explain the observation that most natural resistance to generalist pathogens is  
68 highly polygenic, and the underlying plant genes for resistance are quantitative  
69 (Glazebrook 2005, Nomura, Melotto et al. 2005, Goss and Bergelson 2006, Rowe and  
70 Kliebenstein 2008, Barrett, Kniskern et al. 2009, Corwin, Copeland et al. 2016). Plant  
71 quantitative resistance genes to generalist pathogens include a broad array of direct  
72 defense genes, like those involved in secondary metabolite production, cell wall  
73 formation, and defense proteins (Zhang, Khan et al. 2002, Denby, Kumar et al. 2004,  
74 Zipfel, Robatzek et al. 2004, Ferrari, Galletti et al. 2007, Rowe and Kliebenstein 2008,  
75 Poland, Balint-Kurti et al. 2009, Corwin, Copeland et al. 2016). Importantly, these  
76 quantitative plant resistance loci do not alter resistance to all genotypes (isolates) of a  
77 pathogen but interact with the infecting pathogen's genotype. For example, the ability of  
78 the *Arabidopsis* defense metabolite, camalexin, to provide resistance to *Botrytis cinerea*  
79 depends upon whether the specific isolate is sensitive or resistant to camalexin  
80 (Kliebenstein, Rowe et al. 2005, Pedras and Ahiaonu 2005, Stefanato, Abou-Mansour  
81 et al. 2009, Pedras, Hossain et al. 2011) and similarly *B. cinerea* virulence on tomato  
82 varies with the isolate's ability to detoxify tomatine (Quidde, Osbourn et al. 1998,

83 Quidde, Büttner et al. 1999). In contrast to the polygenic nature of plant resistance to  
84 generalist pathogens, little is known about the genetic architecture of virulence within  
85 generalist pathogens, and how this is affected by genetic variation in the plant (Bartoli  
86 and Roux 2017). There are no reported naturally variable large-effect virulence loci in  
87 generalist pathogens, suggesting that virulence in generalist pathogens is largely  
88 quantitative and polygenic. This potential for interaction between polygenic virulence in  
89 generalist pathogens and equally polygenic resistance in host plants suggests that we  
90 need to work with genetic variation in both the host and pathogen to truly understand  
91 quantitative host-pathogen interactions.

92 A key evolutionary process in plants that has affected resistance to specialist  
93 pathogens is the domestication of crop plants. Domesticated plant varieties are typically  
94 more sensitive to specialist pathogens than their wild relatives (Smale 1996, Rosenthal  
95 and Dirzo 1997, Couch, Fudal et al. 2005, Dwivedi, Upadhyaya et al. 2008), and  
96 pathogens may evolve higher virulence on domesticated hosts (Stukenbrock and  
97 McDonald 2008). Further, domestication typically imposes a genetic bottleneck that  
98 reduces genetic diversity in the crop germplasm, including decreased availability of  
99 resistance alleles against specialist pathogens (Tanksley and McCouch 1997, Doebley,  
100 Gaut et al. 2006, Chaudhary 2013). These general evolutionary patterns, of lower  
101 resistance and allelic diversity found when studying the interaction of specialist  
102 pathogens with crop plants, are assumed to similarly hold for generalist pathogens and  
103 their domesticated hosts. However, there is less information about how crop host  
104 domestication affects disease caused by generalist pathogens, when the resistance to  
105 these pathogens is quantitative and polygenic rather than qualitative and monogenic. As  
106 such, there is a need to conduct a detailed analysis of how domestication may alter the  
107 interaction of a plant with a broad generalist pathogen, and correspondingly, how  
108 domestication influences the pathogen.

109 *Botrytis cinerea* provides a model generalist pathogen for studying quantitative  
110 interactions with plant hosts and underlying evolutionary processes for this generalist in  
111 contrast to specialist pathogens. *B. cinerea* is a broad generalist pathogen that can  
112 infect most tested plants from bryophytes to eudicots and causes wide ranging pre- and  
113 post-harvest crop losses (Nicot and Baille 1996, Elad, Williamson et al. 2007, Fillinger

and Elad 2015). Individual isolates of *B. cinerea* show the same broad host range (Deighton, Muckenschnabel et al. 2001, Finkers, van Heusden et al. 2007, Ten Have, van Berloo et al. 2007, Corwin, Subedy et al. 2016), in contrast to pathogens like *Fusarium oxysporum* where the species can infect diverse hosts, but each isolate is highly host specific (Katan 1999, Ormond, Thomas et al. 2010, Loxdale, Lushai et al. 2011, Barrett and Heil 2012). *B. cinerea* isolates display significant variation in virulence phenotypes, partly due to genetic variation in specific virulence mechanisms, like the production of the phytotoxins, botrydial and botcinic acid (Siewers, Viaud et al. 2005, Dalmais, Schumacher et al. 2011). This genetic variation also influences cell wall degrading enzymes and key regulators of virulence like *VELVET* that quantitatively control virulence on multiple host plants (Rowe and Kliebenstein 2007, Schumacher, Pradier et al. 2012). This genetic variation in diverse virulence mechanisms can contribute to the formation of quantitative differences in virulence between the isolates (ten Have, Mulder et al. 1998). The phenotypic variation is driven by a high level of sequence diversity spread across the genome (Rowe and Kliebenstein 2007, Fekete, Fekete et al. 2012). The polymorphism rate in *B. cinerea* was measured as 6.6 SNP/kb, which is more variable than most previously studied plant pathogens (1-2 SNP/kb in *Blumeria graminis*, 1.5 SNP/kb in *Melampsora larici-populina*, 5.5 SNP/kb in the compact genome of the obligate biotroph *Plasmodiophora brassicae*), and close to the genetic diversity found in the human pathogen *Mycobacterium tuberculosis* (2.9 to 6.2 SNP/kb) (Farhat, Shapiro et al. 2013, Hacquard, Kracher et al. 2013, Wicker, Oberhaensli et al. 2013, Persoons, Morin et al. 2014, Desjardins, Cohen et al. 2016, Power, Parkhill et al. 2017). Higher polymorphism rates are reported for the wheat stem rust pathogen *Puccinia graminis* f. sp. *tritici*, from a small non-random sample of isolates (12.3 SNP/kb) (Upadhyaya, Garnica et al. 2014). In addition to SNP diversity, the genomic sequencing showed that *B. cinerea* has a high level of recombination and genomic admixture, as if it were a randomly intermating population. As such, a collection of *B. cinerea* isolates contains genetic variation in a wide range of virulence mechanisms, offering the potential to challenge the host with a blend of diverse virulence mechanisms. This can potentially identify the pathogen variation controlling quantitative virulence, even in non-model plant systems (Bartoli and Roux 2017).

145 A model pathosystem for studying quantitative host-pathogen interactions during  
146 domestication is the tomato-*B. cinerea* system, where the pathogen causes crop loss  
147 due to both pre- and post-harvest infection (Dean, Van Kan et al. 2012, Hahn 2014,  
148 Romanazzi and Droby 2016). Resistance to *B. cinerea* is a quantitative trait in tomato  
149 as with most other species, with identified tomato QTLs each explaining up to 15% of  
150 phenotypic variation for lesion size on stems (Diaz, ten Have et al. 2002, Finkers, van  
151 Heusden et al. 2007, Ten Have, van Berloo et al. 2007, Rowe and Kliebenstein 2008,  
152 Corwin, Copeland et al. 2016). Tomato is also a key model system to study how  
153 domestication influences plant physiology and resistance, including alterations in the  
154 circadian clock (Tanksley 2004, Bai and Lindhout 2007, Panthee and Chen 2010,  
155 Bergougnoux 2014, Müller, Wijnen et al. 2016), which can modulate resistance to *B.*  
156 *cinerea* (Sauerbrunn and Schlaich 2004, Weyman, Pan et al. 2006, Bhardwaj, Meier et  
157 al. 2011, Hevia, Canessa et al. 2015). This suggests that host plant domestication  
158 within tomato can alter traits known to influence *B. cinerea* resistance from other  
159 systems. Tomato domestication is typically considered a single event, followed by  
160 extensive crop improvement (Lin, Zhu et al. 2014, Blanca, Montero-Pau et al. 2015).  
161 Thus, we are using the tomato-*B. cinerea* pathosystem to directly measure the  
162 interaction of crop domestication with genetic variation in a generalist pathogen to better  
163 understand the evolution of this pathosystem.

164 In this study, we infected 97 genetically diverse *B. cinerea* isolates on a collection  
165 of domesticated tomato, *S. lycopersicum*, and wild tomato, *S. pimpinellifolium*, and  
166 quantified the interaction through lesion size in a detached leaf assay. Previous studies  
167 have examined *B. cinerea* resistance between domesticated and distantly related wild  
168 tomato species (i.e. *S. lycopersicum* and *S. pimpinellifolium*) using single isolates of  
169 pathogens (Egashira, Kuwashima et al. 2000, Nicot, Moretti et al. 2002, Guimaraes,  
170 Chetelat et al. 2004, Ten Have, van Berloo et al. 2007, Finkers, Bai et al. 2008). These  
171 previous studies typically used individual wild and domesticated tomato accessions that  
172 were the founders of mapping populations and found a wide range of *B. cinerea*  
173 resistance. However, it is still unknown how domesticated and closely related wild  
174 tomatoes compare for *B. cinerea* resistance using multiple plant genotypes and a  
175 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- 20<sup>th</sup> 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. We looked for evidence of specialization within our generalist pathogen population. While our *B. cinerea* isolates appear to be generalists across domestication in *Solanum*, a subset of isolates is sensitive to tomato domestication. Finally, we aimed to identify the genetic basis of variation in *B. cinerea* virulence on domesticated and wild tomato. We conducted genome-wide association (GWA) in *B. cinerea* to identify pathogen loci where genetic variation leads to altered virulence across the host genotypes, including a specific test for loci that influence responses to crop domestication. Few studies have conducted GWA in plant pathogens for virulence phenotypes, and most of these were limited by few variable loci or few genetically distinct isolates (Dalman, Himmelstrand et al. 2013, Gao, Liu et al. 2016, Talas, Kalih et al. 2016, Wu, Sakthikumar et al. 2017). To ensure that genetic inference was independent of the GWA method or SNP diversity reference, we repeated genetic analysis with two different association methods (bigRR and GEMMA) using SNPs called in comparison to two published *B. cinerea* genomes (T4 and B05.10). All methods converged on the same image of genetic architecture; virulence of *B. cinerea* is highly quantitative, with hundreds of significant SNPs with small effect sizes associated with lesion area on each tomato genotype. Importantly, there is a subset of loci in the pathogen where allelic variation gives the isolates opposing responses to crop domestication. These pathogen loci could provide tools for understanding how domestication in tomato has influenced generalist pathogen resistance, to inform breeding efforts.

202  
203

204 **Results**

205 **Experimental Design**

206 To measure how tomato domestication affects quantitative resistance to a  
207 population of a generalist pathogen, we infected a collection of 97 diverse *B. cinerea*  
208 isolates (genotypes) on wild and domesticated tomato genotypes. We compared  
209 domesticated and closely related wild tomatoes for *B. cinerea* resistance using multiple  
210 plant genotypes and a population of the pathogen. We selected 6 domesticated  
211 *Solanum lycopersicum* and 6 wild *S. pimpinellifolium* accessions, the closest wild  
212 relative of *S. lycopersicum*, to directly study how domestication has influenced  
213 resistance to *B. cinerea* (Peralta, Spooner et al. 2008, Müller, Wijnen et al.  
214 2016)(Supplemental Figure 1). Our previously collected *B. cinerea* sample includes 97  
215 isolates obtained from various eudicot plant hosts, including tomato stem tissue (2  
216 isolates; T3, KT) and tomato fruit (3 isolates; KGB1, KGB2, Supersteak). We infected all  
217 97 *B. cinerea* isolates onto each of the 12 plant genotypes in 3-fold replication across 2  
218 independent experiments in a randomized complete block design, giving 6  
219 measurements per plant-pathogen combination, for a total of 3,276 lesions. Digital  
220 measurement of the area of the developing lesion provides a composite phenotype  
221 controlled by the interaction of host and pathogen genetics. This measurement of the  
222 plant-*B. cinerea* interaction has been used successfully in a number of molecular and  
223 quantitative genetic studies (Ferrari, Plotnikova et al. 2003, Denby, Kumar et al. 2004,  
224 Kliebenstein, Rowe et al. 2005, Ferrari, Galletti et al. 2007, Ten Have, van Berloo et al.  
225 2007, AbuQamar, Chai et al. 2008, Rowe and Kliebenstein 2008, Liu, Hong et al. 2014).  
226 It should be noted that we are not focusing on MAMP or PAMP specific host/pathogen  
227 interactions with this study, we are instead allowing the identification of any mechanism  
228 that may influence the host/pathogen interaction including metabolism, development or  
229 any other unknown component. If there is genetic variation affecting the trait, and the  
230 trait influences the interaction of host and pathogen, it will be a component of the  
231 experiment. This fits with the recently developing view that growth, development and  
232 resistance in plants are highly integrated processes that may not be as distinct as once  
233 believed (Campos, Yoshida et al. 2016, Ballaré and Pierik 2017, Züst and Agrawal  
234 2017, Izquierdo-Bueno, González-Rodríguez et al. 2018).

235

236 **Lesion size (phenotypic) variation**

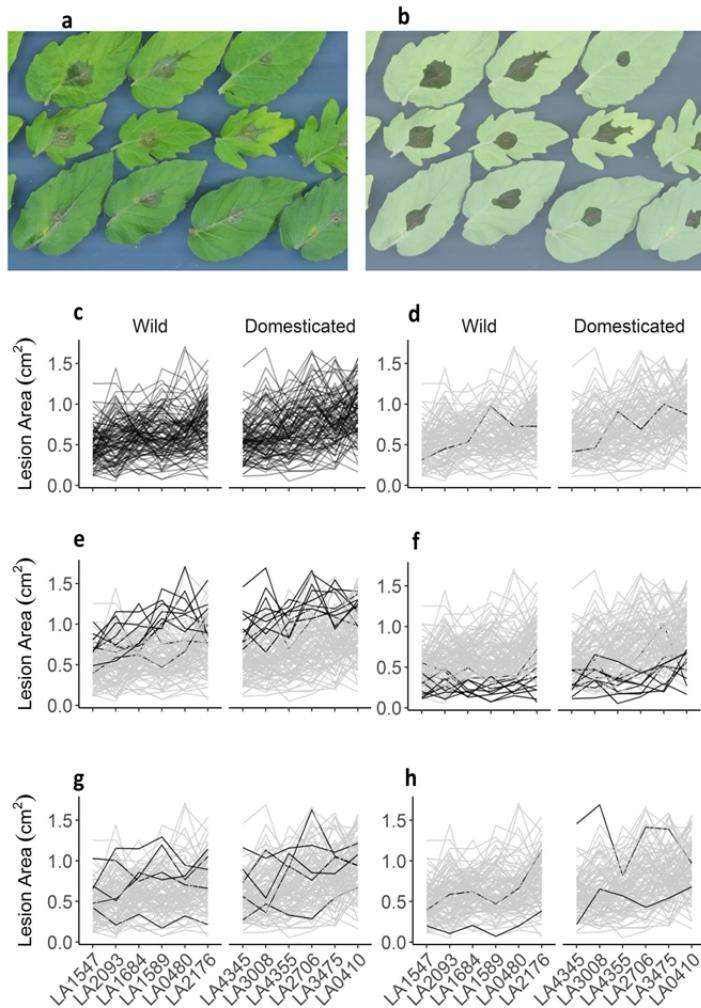
237 We collected images of all lesions at 24, 48, and 72 hours post inoculation. At 24  
238 hours, no visible lesions were present on the tomato leaves. At 48 hours, a thin ring of  
239 primary lesion became visible surrounding the location of the spore droplet, but no  
240 expansion was visible. At 72 hours significant lesion growth was visible, but no lesions  
241 had spread to infect over half of the leaflet. We digitally measured the area of all  
242 developing lesions at 72 hours post infection (HPI) as a measure of virulence (Figure 1).  
243 We observed a mean lesion size of  $0.67 \text{ cm}^2$  across the full experiment, with 0.94 CV  
244 across the full isolate population on all tomato genotypes. Individual isolates were highly  
245 variable in their lesion size across tomato genotypes (Figure 1 c-h), with mean lesion  
246 size per isolate of  $0.14 \text{ cm}^2$  to  $1.29 \text{ cm}^2$ , and individual isolate coefficient of variation  
247 (CV) from 0.51 to 1.68 across all observations on all tomato genotypes (Supplemental  
248 Data Set 1). A subset of these isolates is highly virulent on tomato (mean lesion size >  
249  $1.05 \text{ cm}^2$ , Figure 1e), and a subset can be considered saprophytic (mean lesion size <  
250  $0.3 \text{ cm}^2$ , Figure 1f).

251

252 **Contribution of Pathogen Genetics, Plant Genetics and Crop Domestication**

253 **Effects on Resistance**

254 To measure the relative contribution of genetic diversity in the plant and the  
255 pathogen to variation in the virulence/ susceptibility phenotype, we used a multiple  
256 linear regression model (R Development Core Team 2008). This model directly tested  
257 the contribution of plant genotype, plant domestication status, and pathogen genotype  
258 (isolate) to variation in lesion size. The final model showed that genetic variation within  
259 both the host plant and the pathogen had significant effects on lesion growth, with  
260 pathogen isolate diversity explaining 3.5 fold more variance than plant genotype, 46% of  
261 total genetic variance for pathogen isolate vs. 13% for plant genotype (Table 1 and  
262 Figure 1c). Interestingly, tomato domestication status significantly impacted *B. cinerea*  
263 virulence, as shown by the small but significant effects of genetic variation between  
264 domesticated and wild tomatoes (3.5% of total genetic variance, Table 1). There was no  
265 evidence for significant interaction effects between pathogen isolate and plant



**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.

267 lesion size (34% of total genetic variance, Table 1). The lack of significance for this term  
268 in face of the large fraction of variance may be due to the vast degrees of freedom in  
269 this term (Table 1). Thus, the interaction between tomato and *B. cinerea* was  
270 significantly controlled by genetic diversity within the host plant and the pathogen,  
271 including a slight effect of domestication status.

272

273 **Table 1. ANOVA results of the interaction between 12 tomato accessions and 95**  
274 ***B. cinerea* isolates measured as lesion area.**

275 The Type III Sums-of-Squares, F-value, Degrees of Freedom and p-value for the linear  
276 modelling of lesion area for 12 tomato accessions by 95 *B. cinerea* isolates is shown.  
277 Two of our 97 isolates did not have replication across 2 experiments, so they were  
278 dropped at this stage of analysis. The terms are as follows; Isolate is the 95 *B. cinerea*  
279 isolates, Domestication is wild tomato, *S. pimpinellifolium*, versus domestic tomato, *S.*  
280 *lycopersicum*, Plant is 12 tomato genotypes nested within their respective domestication  
281 groupings, Experiment tests the 2 independent replicate experiments, Experiment/Block  
282 tests the three blocks nested within each experiment. In addition, interactions of these  
283 factors are tested (:).

284

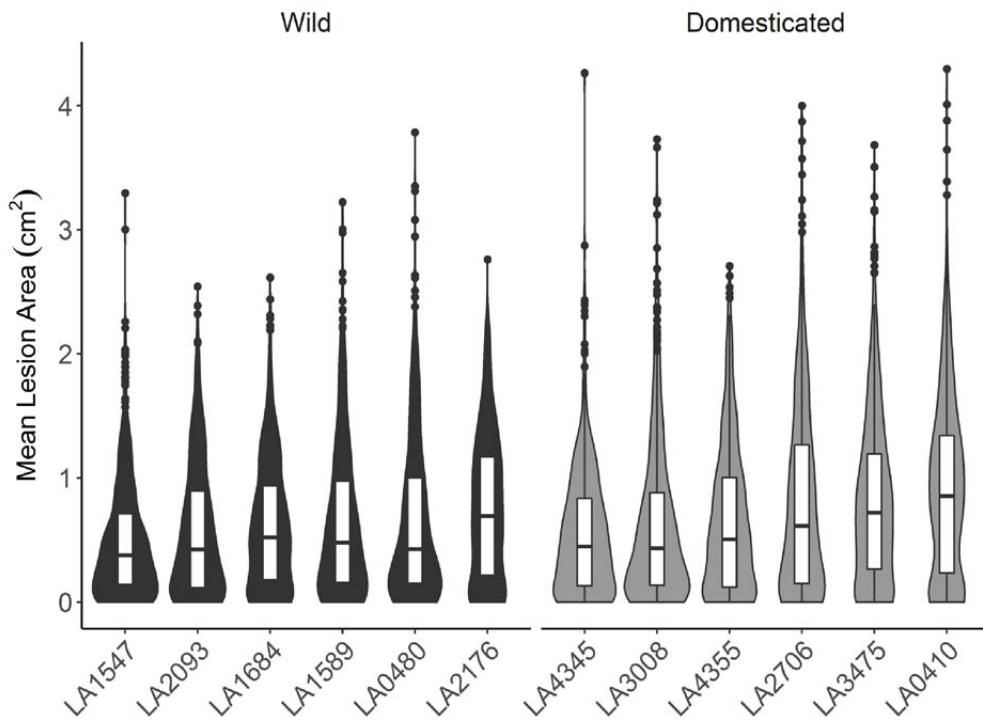
Fixed Effect	% total variance	% genetic variance	SS	F value	DF	p
Isolate	10.2	45.8	256.6	13.5	94	<2e-16
Domestication	0.8	3.5	19.5	96.5	1	<2e-16
Domest/Plant	2.9	13.2	73.7	36.5	10	<2e-16
Iso:Domest	0.8	3.7	20.7	11	94	0.260
Iso:Domest/Plant	7.5	33.8	189.5	1.0	940	0.623
Experiment	21.7		545.7	2707	1	<2e-16
Exp/Block	8.0		201.0	249.3	4	<2e-16
Exp:Iso	6.0		152.2	8.0	94	<2e-16
Exp:Domest	0.03		0.8	4.1	1	0.043
Exp:Domest/Plant	1.9		47.4	23.5	10	<2e-16
Residuals	40.1		1009			

285

286

287 **Domestication and Lesion Size Variation**

288 Existing literature predominantly reports that crop domestication decreases plant  
289 resistance to pathogens (Smale 1996, Rosenthal and Dirzo 1997, Couch, Fudal et al.  
290 2005, Dwivedi, Upadhyaya et al. 2008, Stukenbrock and McDonald 2008). In our  
291 analysis, we identified a significantly greater (18%) resistance of wild tomato in



**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 75<sup>th</sup> 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.

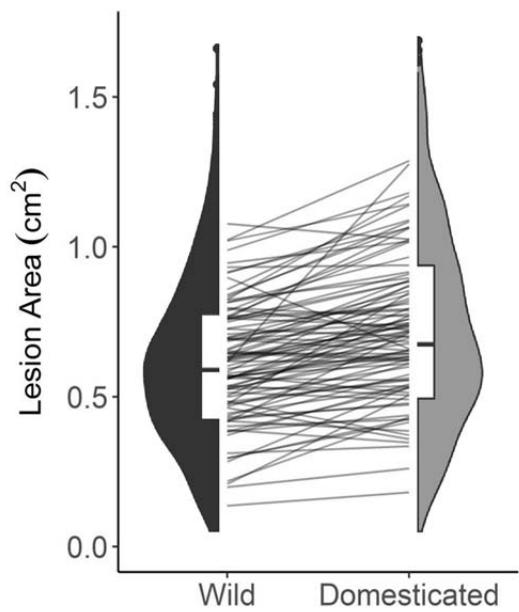
293 2 and 3, Table 1). However, this domestication effect was not the dominant source of  
294 variation, as genetic variation within the domesticated and wild genotypes contributed  
295 3.8-fold more variation in resistance than domestication alone (Table 1). While we did  
296 observe the expected decreased resistance in domesticated tomato, domestication was  
297 a minor player in controlling lesion size variation, with most of the plant genetic  
298 signature coming from variation within both the wild and domesticated tomato species.

299 In addition to altering trait means, domestication commonly decreases genetic  
300 variation in comparison to wild germplasm due to bottlenecks, including for tomato  
301 (Tanksley and McCouch 1997, Doebley, Gaut et al. 2006, Bai and Lindhout 2007). We  
302 would expect this decreased genetic variation to limit phenotypic variation, including  
303 disease phenotypes. Interestingly in this tomato population, we did not observe reduced  
304 variation in lesion size in the wild tomato. Rather, the domesticated tomato genotypes  
305 had a wider range of average lesion size than wild genotypes; the 90<sup>th</sup> percentile range  
306 (95<sup>th</sup> percentile to 5<sup>th</sup> percentile) spanned 2.03 cm<sup>2</sup> lesion size variation on  
307 domesticated tomato (standard deviation = 0.68 cm<sup>2</sup>) versus 1.76 cm<sup>2</sup> variation on wild  
308 tomato (standard deviation = 0.58 cm<sup>2</sup>). Additionally, the wild and domesticated tomato  
309 genotypes showed statistically similar variation in resistance (F-test, F<sub>96,96</sub>=1.39,  
310 p=0.11) (Figure 3, Supplemental Figure 1). Overall, there is a slight domestication  
311 impact on average resistance to *B. cinerea*, but no evidence of a phenotypic bottleneck  
312 due to domestication.

313

### 314 **Pathogen Specialization to Source Host**

315 One evolutionary model of plant-generalist pathogen interactions suggests that  
316 generalist pathogen isolates within a species may specialize for interaction with specific  
317 hosts. Alternatively, generalist isolates may show no host specialization or preference.  
318 Our collection of *B. cinerea* includes five isolates that may be adapted to tomato, as  
319 they were collected from *S. lycopersicum*. To test if there is evidence for specialization  
320 to the source host, we compared the virulence of the *B. cinerea* isolates obtained from  
321 tomato to the broader pathogen population. For *B. cinerea* genotypes isolated from  
322 tomato tissue vs. other hosts, there was no significant difference in lesion size on  
323 domesticated tomato (t-test; t=1.10, n = 97, p=0.33), wild tomato (t-test; t=1.09, n = 97,



**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,  $p<2e-16$ ). 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.

325 isolate collected from tomato tissue (KGB1) was within the 10 least-virulent isolates and  
326 another (Triple3) was within the 10 most-virulent isolates (Figure 1g). This  
327 demonstrated significant genetic variation in virulence across the *B. cinerea* isolates,  
328 and that this collection of *B. cinerea* isolates from tomato do not display a strong host-  
329 specificity for tomato (Martinez, Blancard et al. 2003, Ma and Michailides 2005, Rowe  
330 and Kliebenstein 2007, Samuel, Veloukas et al. 2012).

331

### 332 **Pathogen Specialization to Host Genotype**

333 Though we did not find evidence for *B. cinerea* adaptation to tomato based on  
334 isolate host source, the *B. cinerea* isolates may contain genetic variation at individual  
335 loci that allow them to better attack subsets of the tomato genotypes (Rowe and  
336 Kliebenstein 2007, Kretschmer and Hahn 2008, Corwin, Subedy et al. 2016). A visual  
337 analysis of the data suggested an interaction between the genomes of *B. cinerea* and  
338 tomato (Figure 1 c-h). However, when using the full model, we found no significant  
339 interaction between isolate and individual host genotype, even though there was a large  
340 fraction of variance within these terms (Table 1). This may indicate a lack of interaction  
341 between genetic variation in the host and pathogen. Interaction effects in large datasets  
342 can be difficult to identify using mixed models, so we used a second standard statistical  
343 approach, a Wilcoxon signed-rank test, to test if the rank of *B. cinerea* isolate-induced  
344 lesion size significantly changes between pairs of tomato genotypes. This showed that  
345 when using the full isolate population, the rank performance of the isolates does  
346 significantly vary between host genotypes. When comparing mean lesion size between  
347 paired plant genotypes, 58% (38 out of 66) of tomato accession pairs had significantly  
348 different ranking of the isolates (Wilcoxon signed-rank test with Benjamini-Hochberg  
349 FDR-correction, Table 2, Supplemental Figure 2). A significant p-value indicates that the  
350 two host genotypes show evidence for different virulence interactions with the  
351 population of *B. cinerea* isolates, providing evidence for host x pathogen genotypic  
352 interactions. This pattern was consistent across domesticated host pairs, wild host  
353 pairs, or between-species host pairs (Wilcoxon signed-rank test with B-H FDR-  
354 correction, Table 2). This suggests that the population of *B. cinerea* does display  
355 differential responses to the tomato genetic variation.

356 To focus on whether specific *B. cinerea* isolates may be sensitive to  
357 domestication, we applied a Wilcoxon and ANOVA approach. Overall, most isolates  
358 (78/97, 80%) are more virulent on domesticated than wild tomato (Figure 3). The  
359 Wilcoxon signed-rank test, to compare the rank of mean lesion size of all the *B. cinerea*  
360 isolates on wild versus domesticated tomato, was significant (Wilcoxon signed-rank test,  
361  $W = 5946$ , p-value = 0.002) (Figure 3). To identify the pathogen genotypes most  
362 sensitive to domestication, we conducted single-isolate ANOVAs including the fixed  
363 effects of plant, domestication, and experiment, and found two isolates with a significant  
364 effect of domestication on lesion size ( $p < 0.05$ , FDR corrected) (Figure 1h), both of  
365 which are more virulent on domesticated tomato. These included one of the highly  
366 virulent isolates (Fd2), and one of the largely saprophytic isolates (Rose), which  
367 suggests that isolate virulence level on tomato does not predict *B. cinerea* genetic  
368 response to tomato domestication. Both of these isolates were more virulent on  
369 domesticated than on wild tomato. These results suggest that this *B. cinerea* population  
370 contains two highly domestication-sensitive isolates which are more virulent on  
371 domesticated tomato, and a broader pattern of *B. cinerea* sensitivity to tomato genetic  
372 variation.

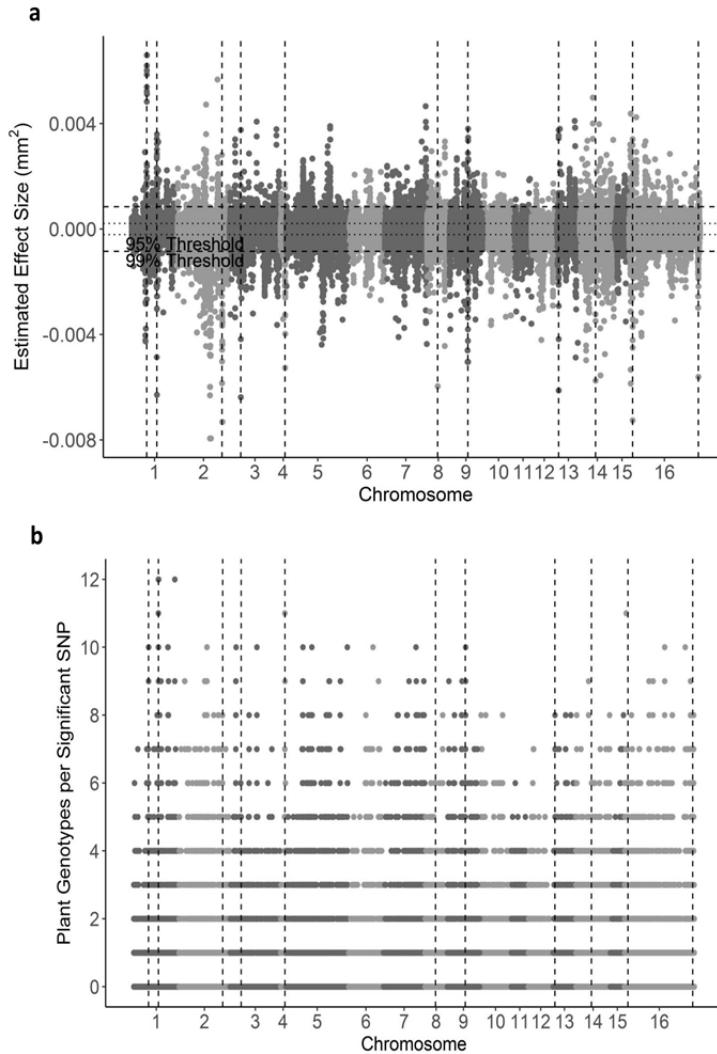
373  
374

375 **Table 2. Rank order shifts of 97 *B. cinerea* isolates by lesion area across all of the**  
 376 **tomato accessions.**

377 Wilcoxon signed-rank test comparing mean *B. cinerea* lesion area on tomato  
 378 accessions. This tests for a change in the rank order of the 97 isolates between each  
 379 pair of tomato accessions. A significant p-value suggests that the relative performance  
 380 of individual isolates is altered from one host to the other. The lower left corner of the  
 381 chart includes B-H FDR-corrected p-values, the upper right corner includes the test  
 382 statistic (W). Bold text indicates significance at  $p < 0.01$  after correction, italicized text  
 383 indicates suggestive p-values  $0.01 < p < 0.1$ . NS shows non-significant interactions.  
 384

			Wild					Domesticated									
			LA1547	LA1589	LA1684	LA2093	LA2176	LA480	LA2706	LA3008	LA3475	LA410	LA4345	LA4355			
Wild					3256	3975	3069	2228	3006	2165	3478	1847	1253	3942	2970		
				<0.001		5323	4755	3566	4563	3396	4860	3173	2406	5491	4426		
			LA1684	LA1589	0.086	NS	4020	3008	3926	2885	4194	2627	1959	4776	3810		
			LA2093	LA2176	<0.001	NS	NS		3395	4575	3260	4943	2919	2093	5630	4384	
			LA2176	LA480	<0.001	0.007	<0.001	0.002		5766	4428	5955	4287	3411	6670	5610	
			LA480	LA2706	<0.001	NS	0.067	NS	0.012		5939	4376	6212	6999	3703	4869	
Domesticated					<0.001	0.002	<0.001	0.001	NS	0.003		6071	4564	3785	6716	5794	
				LA3008	LA3475	0.003	NS	NS	NS	0.003	NS	0.001		3062	2339	5309	4283
			LA3475	LA410	<0.001	<0.001	<0.001	<0.001	NS	<0.001	NS	<0.001		3824	7088	6022	
			LA410	LA4345	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	0.030	<0.001	0.037		7779	6820	
			LA4345	LA4355	0.072	0.065	NS	0.030	<0.001	0.018	<0.001	0.158	<0.001	<0.001		3601	
			LA4355		<0.001	NS	0.034	NS	0.032	NS	0.010	NS	0.002	<0.001	0.009		

385  
 386  
 387 **Quantitative Genetics of Pathogen Virulence on Tomato**  
 388 Genetic variation within *B. cinerea* had a large effect on virulence on tomato and  
 389 interacted with tomato domestication (Table 1). This suggests that there is genetic  
 390 variation within the pathogen, in which some alleles enhance, and other alleles  
 391 decrease virulence depending upon the plant's genotype. To identify variable pathogen



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

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

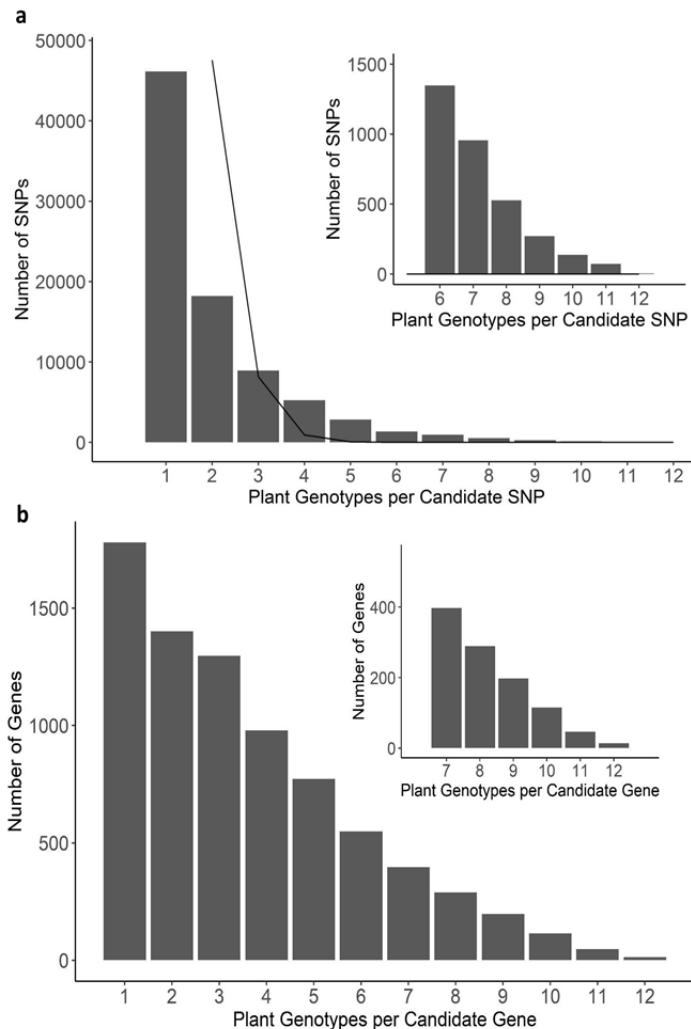
a) Manhattan plot of estimated SNP effect sizes from bigRR for *B. cinerea* lesion size using a single tomato accession, LA2093. Permutation-derived thresholds are shown in horizontal dashed lines.

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 ( $\geq 6$ ) of tomato genotypes tested.

392 genes controlling differential virulence across plant genotypes, we conducted GWA

mapping analysis within the pathogen by two approaches. Due to the large effect of plant genotype on resistance to *B. cinerea*, we performed GWA using the model-corrected least-squared mean virulence measured on each tomato genotype as separate traits. We first used a ridge-regression approach (bigRR) in combination with 272,672 SNPs from *B. cinerea* compared to the T4 reference genome to estimate the phenotypic effects across the genome (Shen, Alam et al. 2013, Corwin, Copeland et al. 2016, Corwin, Subedy et al. 2016, Francisco, Joseph et al. 2016). To verify these patterns, we also implemented a Genome-wide Efficient Mixed-Model Association (GEMMA) analysis with a centered relatedness matrix to control for the effects of population structure (Zhou and Stephens 2012). In GEMMA, we included 237,878 SNPs from *B. cinerea* compared to the B05.10 reference genome. To determine significance of SNP effects under both GWA methods, we permuted phenotypes 1000 times to calculate 95, 99, and 99.9% effect size thresholds within each plant host. Under both methods, GWA analysis showed that the genetic basis of *B. cinerea* virulence on tomato is highly polygenic. Consistent with a polygenic structure of this trait in the pathogen, neither method of GWA identified large-effect SNPs (Figure 4). The ridge-regression approach (bigRR) identified from 1,284 to 25,421 SNPs within *B. cinerea* that were significantly associated with altered virulence on the 12 different host genotypes (significance was determined by the SNP effect size estimate exceeding the 99% 1000-permutation threshold). The model accounting for population structure (GEMMA) confirmed our finding of a highly polygenic nature of lesion size in the pathogen (Supplemental Figure 3), with 2,530 to 8,221 SNPs significantly associated with virulence at the 99% threshold, and 288 to 1,361 SNPs at the 99.9% threshold (significance was determined using an empirically determined 1000-permutation threshold).

To focus on the small-effect genes linked to *B. cinerea* virulence, we classified a gene as significantly associated if there was 1 SNP linked to a trait using a 2kbp window surrounding the start and stop codon for a given gene. This analysis identified 14 genes linked to differential virulence in all 12 tomato accessions by bigRR (Figure 5b, Supplemental Data 2 e), as some SNPs within a gene had accession-specific phenotypes (significant in <12 tomato accessions). A further 1045 genes were linked to



**Figure 5. Frequency of overlap in *B. cinerea* GWA significance across tomato accessions.**

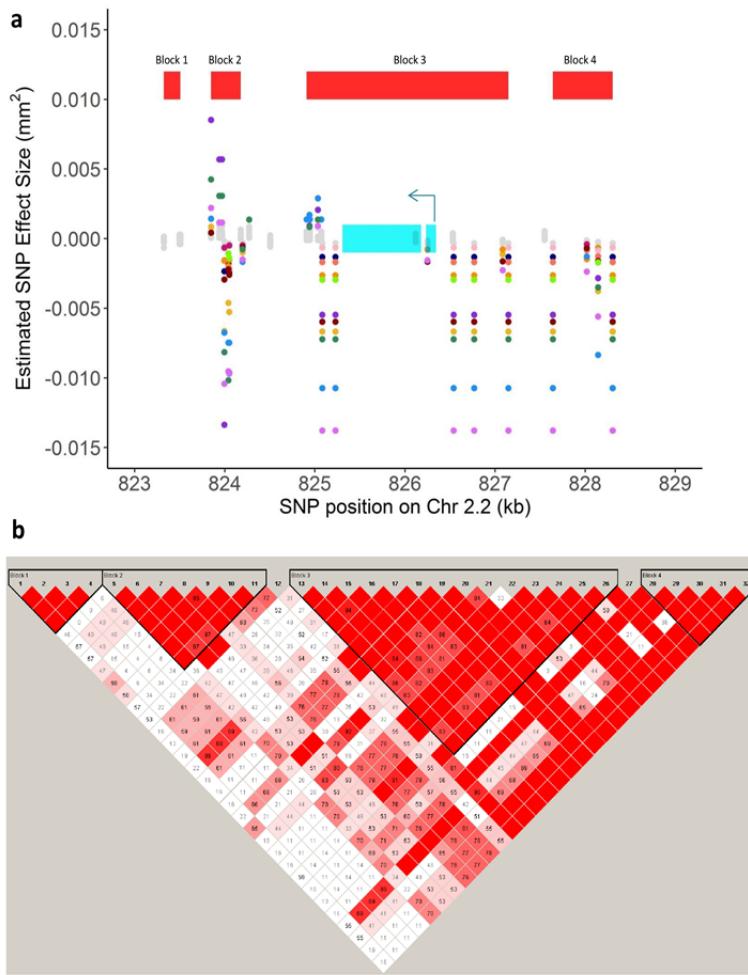
a) The frequency with which the *B. cinerea* SNPs significantly associate with lesion size on the 12 tomato accessions using bigRR and the 99% permutation threshold. The black line indicates the expected frequency of random overlap, given the number of significant SNPs per plant genotype and size of 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.

425 Supplemental Data 2 e). At the 99.9% SNP significance threshold, GEMMA identified  
426 23 genes across 7 to 9 of the tomato accessions (Supplemental Figure 4).

427 Of the 14 genes with SNPs significantly associated with *B. cinerea* virulence on  
428 all tomato genotypes by bigRR, most have not been formally linked to pathogen  
429 virulence. However, SNPs within a pectinesterase gene (BcT4\_6001, Bcin14g00870)  
430 were associated to virulence across 11 tomato accessions. Pectinesterases are key  
431 enzymes for attacking the host cell wall, suggesting that variation in this pectinesterase  
432 locus and the other loci may influence pathogen virulence across all the tomato  
433 genotypes (Valette-Collet, Cimerman et al. 2003). Therefore, we looked for evidence of  
434 multiple haplotypes in this locus linked to virulence by visualizing the SNP effects  
435 across the pectinesterase gene. We plotted the effect sizes for all SNPs in this gene  
436 and investigated the linkage disequilibrium amongst these SNPs (Figure 6). This  
437 showed that the effect of SNPs across this gene vary in effect direction depending on  
438 tomato host genotype (Figure 6a). We identified two haplotype blocks contributing to the  
439 association of this gene to the virulence phenotype (Figure 6b). One block is associated  
440 with SNPs in the 5' untranslated region in SNPs 5-11, and the second block is SNPs  
441 that span the entirety of the gene in SNPs 13-26. Interestingly, there are only two SNPs  
442 in the open reading frame of the associated gene (Figure 6). This suggests that the  
443 major variation surrounding this locus is controlling the regulatory motifs for this  
444 pectinesterase. Thus, there is significant genetic variation in *B. cinerea* virulence that is  
445 dependent upon the host's genetic background. This suggests that the pathogen relies  
446 on polygenic small effect loci, potentially allowing selection to customize virulence on  
447 the different tomato hosts.

448 To identify genes consistently associated with *B. cinerea* virulence on tomato  
449 across GWA methods, we examined the gene overlap between significant associations  
450 identified by GEMMA on the B05.10 genome and bigRR on the T4 genome. We  
451 conservatively identified genes within 2kb of significant SNPs at the 99% permutation  
452 threshold for bigRR, and at the 99.9% permutation threshold for GEMMA. Among these,  
453 263 genes were linked to at least two plant genotypes by both methods (Supplemental  
454 Data 2 a). These genes include transporters and enzymes that can be important for  
455 *Botrytis* toxin production and/or detoxification of plant defense compounds and are key



**Figure 6. Host specificity of significant SNPs linked to the gene BcT4\_6001 (Bcin14g00870).**

a) SNPs with effects estimates above the 99% permutation threshold are colored by trait (plant phenotype in which the effect was estimated). BcT4\_6001 (Bcin14g00870) is a pectinesterase gene linked to at least one significant SNP on all 12 of the tested tomato accessions by bigRR. The annotated exons are depicted as turquoise rectangles, with the start codon marked with an arrow indicating the direction of transcription. Red rectangles indicate corresponding linkage disequilibrium blocks from Figure 6b.

b) Linkage disequilibrium plot, including all pairwise comparisons of SNPs in the 2kb region surrounding Bcin14g00870. The color scheme for each SNP pair is  $D'/\text{LOD}$ : white if  $\text{LOD} < 2$  and  $D' < 1$ , bright red for  $\text{LOD} \geq 2$  and  $D' = 1$ , intermediate shades for  $\text{LOD} \geq 2$  and  $D' < 1$ .

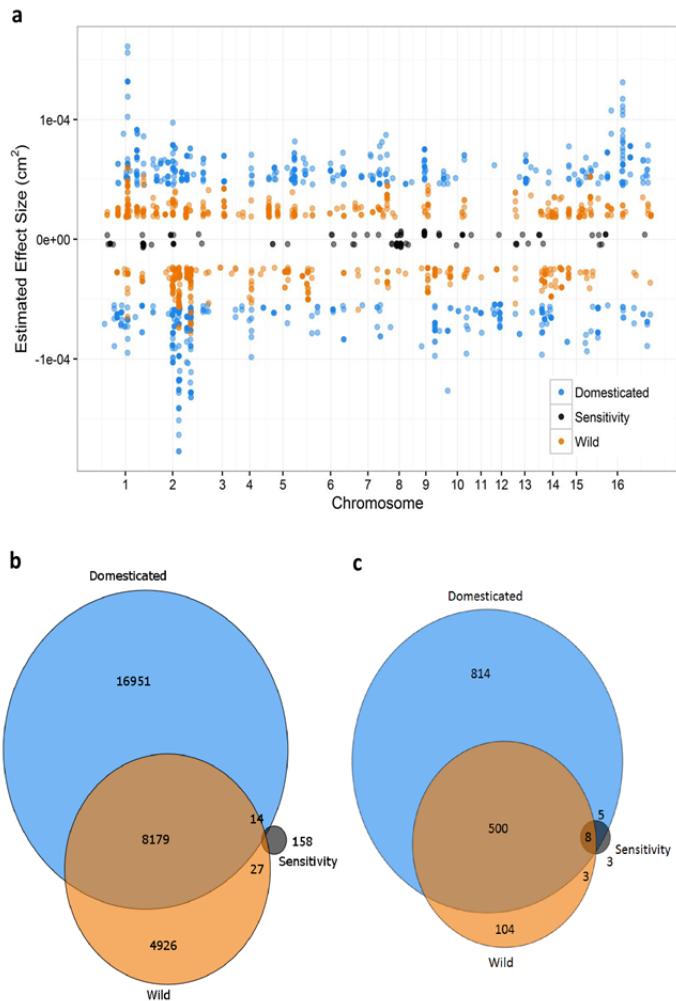
457 identified (Supplemental Data 2 a, c).

458 At the SNP level, fewer loci contribute to virulence across all hosts and both  
459 GWA methods. We found five *B. cinerea* SNPs significantly linked to altered lesion size  
460 on all 12 tomato accessions using the bigRR analysis (Figure 4b). 215 SNPs were  
461 called in at least ten hosts, and 3.3k SNPs were called in at least half of the hosts while  
462 27% (46,000) of the significant SNPs were linked to virulence on only a single host  
463 tomato genotype. These levels of overlap exceed the expected overlap due to random  
464 chance (Figure 5a). GEMMA analysis also found significant SNP overlap between hosts  
465 at the 99% permutation threshold, with 89 SNPs in at least ten hosts, 859 SNPs in at  
466 least half of the hosts, and 63% (19,270) of significant SNPs unique to a single host.  
467 SNP calling between hosts was lower for GEMMA at the 99.9% permutation threshold,  
468 with 78% of significant SNPs (4269) in a single host, and 38 SNPs significant across at  
469 least half of the hosts (Supplemental Figure 4 a). While only a small subset of these *B.*  
470 *cinerea* SNPs were linked to virulence on all the tomato genotypes, we obtained better  
471 overlap across host genotypes by focusing on gene windows.

472

### 473 **Quantitative Genetics of Pathogen Response to Tomato Domestication**

474 The identification of two isolates that distinctly respond to tomato domestication  
475 suggests that there is natural genetic variation in *B. cinerea* that is affected by tomato  
476 domestication. To directly map *B. cinerea* genes that control differential virulence on  
477 wild versus domestic tomatoes, we used the least-squared mean virulence of each  
478 isolate across all wild and all domesticated tomato genotypes as two traits. We also  
479 calculated a domestication sensitivity trait; the relative difference in lesion size for each  
480 isolate between domesticated and wild hosts. Using these three traits, we conducted  
481 bigRR GWA within *B. cinerea* to map genes in the pathogen that respond to  
482 domestication shifts in the plant. Using the mean lesion area of the *B. cinerea* isolates  
483 on the wild or domesticated tomato hosts identified a complex, highly polygenic pattern  
484 of significant SNPs similar to the individual tomato accessions (Figure 4, Figure 7). This  
485 had a high degree of overlap between the wild phenotype and domesticated phenotype.  
486 In contrast, the Domestication Sensitivity trait identified a much more limited set of  
487 SNPs that had less overlap with the mean lesion area on either Domesticated or Wild



**Figure 7. GWA analysis of domestication sensitivity in *B. cinerea*.**

Domestication sensitivity of each isolate was estimated using the average virulence on the wild and domesticated tomato germplasm and using calculated Sensitivity. This was then utilized for GWA mapping by bigRR.

- The top 1000 SNPs that significantly affect lesion size across domesticated tomato, wild tomato or domestication sensitivity are shown. Significance is called as crossing the 99% permutation threshold.
- Venn diagram of overlapping SNPs identified as crossing the 99% permutation threshold for each trait.
- Venn diagram of overlapping genes identified as crossing the 99% permutation threshold for each trait. Genes were called as significant if there was one significant SNP within the gene body or within 2kb of the gene body.

488 tomato (Figure 7). GWA of these domestication traits by GEMMA identified similar

489 patterns of polygenic structure, high overlap between SNPs and genes on wild or  
490 domesticated tomato hosts, and rare overlap with Domestication Sensitivity  
491 (Supplemental Figure 5). To begin querying the underlying gene functions for these  
492 various *B. cinerea* loci, we called genes as significant if there was one SNP within 2kb  
493 of the gene (Figure 7c). We also examined the genes associated with these  
494 domestication virulence traits found by both bigRR and GEMMA. This overlap identified  
495 200 unique genes including several transporters and enzymes, with few predicted  
496 virulence genes (Supplemental Data 2 b). One gene from this overlap list  
497 (Bcin01g05800) contains TPR repeats, which are common in bacterial virulence  
498 proteins (Cerveny, Straskova et al. 2013) and are among the proteins secreted by the  
499 plant pathogen *Ustilago maydis* (Lo Presti, López Díaz et al. 2016). Using all 1251  
500 genes linked to domestication traits by bigRR for a functional enrichment analysis found  
501 only 22 significantly overrepresented biological functions (Fisher exact test,  $p<0.05$ ,  
502 Supplemental Data 2 f) when compared to the whole-genome T4 gene annotation. We  
503 also examined functional enrichment for the genes associated with domestication traits  
504 by both GEMMA and bigRR. We found 41 significantly overrepresented biological  
505 functions (Supplemental Data 2 d). In both datasets, the enrichments were largely  
506 surrounding enzyme and transport functions, which are known to be key components of  
507 how the pathogen produces toxic metabolites and conversely detoxifies plant defense  
508 compounds. Thus, there is an apparent subset of *B. cinerea* genes that may be specific  
509 to the genetic changes that occurred in tomato during domestication. Further work is  
510 needed to assess if and how variation in these genes may link to altered virulence on  
511 domestic and wild tomatoes.

512

513

514      **Discussion**

515      The genetics of plant resistance to generalist pathogens are mostly quantitative,  
516      depend upon pathogen isolate, and rely on genetic variation in both signal perception  
517      and direct defense genes (Kover and Schaal 2002, Parlevliet 2002, Glazebrook 2005,  
518      Nomura, Melotto et al. 2005, Goss and Bergelson 2006, Tiffin and Moeller 2006, Rowe  
519      and Kliebenstein 2008, Barrett, Kniskern et al. 2009, Corwin, Copeland et al. 2016).  
520      Previous studies on tomato resistance to *B. cinerea* have found a quantitative genetic  
521      architecture that varies between domesticated and wild tomato species, with higher  
522      resistance in the wild species (Egashira, Kuwashima et al. 2000, Nicot, Moretti et al.  
523      2002, Guimaraes, Chetelat et al. 2004, Finkers, van Heusden et al. 2007, Ten Have,  
524      van Berloo et al. 2007, Finkers, Bai et al. 2008). However, it was not known how the  
525      choice of *B. cinerea* isolate may change this plant-pathogen interaction. To address  
526      these questions, we used genetic variation in wild and domesticated tomato accessions  
527      in conjunction with a population of *B. cinerea* isolates. This also allowed us to test how  
528      domestication within tomato influenced the interaction at the level of the pathogen  
529      population and individual genes in the pathogen. *B. cinerea* virulence on tomato, as  
530      measured by lesion size, was significantly affected by pathogen isolate, host genotype,  
531      and domestication status (Table 1). Tomato domestication led to a slight but significant  
532      decrease in resistance to the pathogen but critically, there was no evidence of a  
533      domestication bottleneck, with similar variance in resistance between the wild and  
534      domesticated tomato accessions (Table 1, Figure 2). There was also little evidence in  
535      this *B. cinerea* population for specialization to tomato, supporting the hypothesis that *B.*  
536      *cinerea* is a generalist at the isolate and species level (Figure 1 c-h) (Giraud, Fortini et  
537      al. 1999, Martinez, Blancard et al. 2003, Ma and Michailides 2005). GWA mapping  
538      within the pathogen showed that the genetics underlying *B. cinerea* virulence on tomato  
539      are highly quantitative and vary across tomato genotypes and domestication status  
540      (Figure 5, Figure 7). This analysis identified a small subset of pathogen genes whose  
541      variation contributes to differential virulence on most of the hosts tested, and a set of  
542      pathogen genes whose variation is responsive to tomato domestication (Supplemental  
543      Data 2 b, d, f). We also identified a conservative subset of genes whose association to

544 differential *Botrytis cinerea* virulence is consistent across GWA methods and reference  
545 genomes (Supplemental Data 2 a, b, c, d).

546

#### 547 **Domestication and altered pathogen virulence genetics**

548 These results provide evidence of a mild tomato domestication effect on  
549 resistance to the generalist pathogen, *B. cinerea*. We measured an 18% increase in  
550 susceptibility across domesticated varieties, but this represents less than 1% of the total  
551 variance of *B. cinerea* lesion size on tomato (Table 1). As such, domestication status  
552 alone is a poor predictor of a specific tomato host's resistance to infection by *B. cinerea*.  
553 This suggests that while tomato domestication does affect this plant-pathogen  
554 interaction, it is not the primary factor defining the measured trait. The effect of tomato  
555 domestication varied across the *B. cinerea* isolates, with specific loci linked to  
556 differential virulence across wild and domestic tomatoes (Figure 1 c-h). If a study relies  
557 on one or a few isolates, it could obtain a falsely high or falsely low estimation of how  
558 host domestication influences pathogen resistance. This shows the need to utilize a  
559 population of *B. cinerea* to understand the factors contributing to *B. cinerea* virulence  
560 and how this is altered by crop domestication.

561 In biotrophic pathogens, host domestication has decreased the diversity of  
562 resistance alleles because they are lost in the domestication bottleneck as found for  
563 specialist pathogens (Tanksley and McCouch 1997, Doebley, Gaut et al. 2006, Hyten,  
564 Song et al. 2006, Chaudhary 2013). Surprisingly, we did not find evidence for a  
565 domestication bottleneck in the phenotypic resistance to *B. cinerea* (Figure 2, Figure 3).  
566 This is in contrast to genomic studies that explicitly show a genotypic bottleneck within  
567 tomato domestication (Miller and Tanksley 1990, Koenig, Jiménez-Gómez et al. 2013).  
568 This suggests that at least for this generalist pathogen, the genetic bottleneck of tomato  
569 domestication has not imparted a phenotypic bottleneck. One possible explanation is  
570 that resistance to this pathogen is so polygenic in the plant that our experiment is not  
571 sufficiently large to pick up any genetic bottleneck effect using phenotypic variance.  
572 These patterns, of mild decrease in resistance to *B. cinerea* due to plant domestication,  
573 and within-species plant variation exceeding the contribution of domestication itself,  
574 may be unique to interactions between *B. cinerea* and tomato, or more general. It

575 remains to be seen if these patterns hold for *B. cinerea* on its other host plants. It is  
576 unclear whether domestication has a universal effect on plant resistance to *B. cinerea*,  
577 or if each domestication event is unique.

578

### 579 **Polygenic quantitative virulence and breeding complications**

580 Our results indicate a highly polygenic basis of quantitative virulence of the  
581 generalist *B. cinerea* on tomato. The variation in lesion size is linked to numerous *B.*  
582 *cinerea* SNPs, each with small effect sizes (Figure 4a). Importantly, the tomato host  
583 accession greatly influenced which *B. cinerea* loci were significantly associated to lesion  
584 size (Figure 5). Thus, it is possible that there is specialization at the gene level, in which  
585 different alleles within the pathogen link to differential virulence on specific host  
586 genotypes (Giraud, Fortini et al. 1999, Rowe and Kliebenstein 2007, Blanco-Ulate,  
587 Morales-Cruz et al. 2014). This polygenic architecture of virulence is distinctly different  
588 from specialist pathogens that often have one or a few large effect genes that control  
589 virulence (Keen 1992, De Feyter, Yang et al. 1993, Abramovitch and Martin 2004, Boyd,  
590 Ridout et al. 2013, Vleeshouwers and Oliver 2014). Further studies are needed to  
591 compare how the host plant species may affect this image of genetic variation in  
592 virulence.

593 These results indicate particular challenges for breeding durable resistance to *B.*  
594 *cinerea*, and possibly other generalist pathogens. The highly polygenic variation in  
595 virulence, combined with genomic sequencing showing that this pathogen is an inter-  
596 breeding population, suggests that the pathogen is actively blending a large collection of  
597 polymorphic virulence loci (Rowe and Kliebenstein 2007, Fekete, Fekete et al. 2012,  
598 Atwell, Corwin et al. 2015). Thus, it is not sufficient to breed crop resistance against a  
599 single isolate of *B. cinerea*, as this resistance mechanism would likely be rapidly  
600 overcome by new genotypes within the field population of *B. cinerea*. In contrast, it is  
601 likely necessary to breed resistance using a population of the pathogen, and to focus on  
602 plant loci that target entire virulence pathways or mechanisms. The results in this study  
603 indicate that the specific genetics of the plant host, the general domestication status,  
604 and the specific genetics of the pathogen isolate will all combine to affect how the  
605 estimated breeding value inferred from any experiment will translate to a field

606 application (Table 1). As such, utilizing a single or even a few pathogen isolates to  
607 guide resistance breeding in plants is unlikely to translate to durable resistance against  
608 *B. cinerea* as a species. Further, the lack of a domestication bottleneck on tomato  
609 resistance to *B. cinerea* suggests that, at least for tomato, allelic variation in this  
610 generalist pathogen is sufficient to overcome introgression of wild resistance genes or  
611 alleles into the domesticated crop.

612 This study examined the contributions of host and pathogen natural genetic  
613 variation to the quantitative interaction in the tomato-*B. cinerea* pathosystem. In  
614 addition, the study explicitly tested the effects of tomato domestication on this  
615 pathosystem. *B. cinerea* has a highly quantitative genetic basis of virulence on tomato,  
616 which is dominated by pathogen effects but also sensitive to genetic variation linked to  
617 tomato domestication. Future studies are necessary to test if this pattern of  
618 domestication responses in tomato is similar to patterns in other crops. Because this  
619 population of *B. cinerea* can infect a wide range of hosts, it will be possible to directly  
620 conduct this study. By extending future work to additional domestication events, it may  
621 be possible to test whether independent crop domestication events have a consistent  
622 underlying genetic signal of *B. cinerea* adaptation to plant domestication.

623  
624

625 **Methods**

626 **Tomato genetic resources**

627 We obtained seeds for 12 selected tomato genotypes in consultation with the UC  
628 Davis Tomato Genetics Resource Center. These include a diverse sample of 6  
629 genotypes of domesticated tomato's closest wild relative (*S. pimpinellifolium*) sampling  
630 across its major geographic regions (Peru, Ecuador) and 6 heritage and modern  
631 varieties of *S. lycopersicum*, focusing on mid- to late-20<sup>th</sup> century improved varieties  
632 (Lin, Zhu et al. 2014, Blanca, Montero-Pau et al. 2015). While genetic data is not  
633 available for all of our *S. pimpinellifolium* accessions, 9 of the 12 accessions have been  
634 genotyped and span the mappable diversity in domesticated tomato and its close  
635 relatives (Sim, Durstewitz et al. 2012) (Supplemental Figure 1). We bulked all  
636 genotypes in long-day (16h photoperiod) greenhouse conditions at UC Davis in fall  
637 2014. We grew plants under metal-halide lamps using day/night temperatures at  
638 25°C/18°C in 4" pots filled with standard potting soil (Sunshine mix #1, Sun Gro  
639 Horticulture). Plants were watered once daily and pruned and staked to maintain upright  
640 growth. Fruits were collected at maturity and stored at 4°C in dry paper bags until seed  
641 cleaning. To clean the seeds, we incubated seeds and locule contents at 24°C in 1%  
642 protease solution (Rapidase C80 Max) for 2h, then rinsed them in deionized water and  
643 air-dried. We then stored seeds in a cool, dry, dark location until use.

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

655 ontogenetic effects on the pathogen/host interaction in other systems (Corwin,  
656 Copeland et al. 2016).

657

### 658 ***B. cinerea* genetic resources**

659 We utilized a previously described collection of *B. cinerea* isolates that were  
660 isolated as single spores from natural infections of fruit and vegetable tissues collected  
661 in California and internationally (Atwell, Corwin et al. 2015, Zhang, Corwin et al. 2017).  
662 This included five isolates obtained from natural infections of tomato. We maintained *B.*  
663 *cinerea* isolates as conidial suspensions in 30% glycerol for long-term storage at -80°C.  
664 For regrowth, we diluted spore solutions to 10% concentration in filter-sterilized 50%  
665 grape juice, and then inoculated onto 39g/L potato dextrose agar (PDA) media. We  
666 grew isolates at 25°C in 12h light and propagated every 2 weeks. Sequencing failed for  
667 6 out of our 97 phenotyped isolates. For bigRR GWA mapping with the 91 isolates  
668 genotyped in this study, we utilized a total of 272,672 SNPs against the *B. cinerea* T4  
669 genome with minor allele frequency (MAF) 0.20 or greater, and less than 10% missing  
670 calls across the isolates (SNP calls in at least 82/ 91 isolates). For GEMMA mapping,  
671 we used 91 isolates with a total of 237,878 SNPs against the *B. cinerea* B05.10 genome  
672 with MAF 0.20 or greater and less than 10% missing calls. The overall SNP number  
673 was similar when using either reference genome.

674

### 675 **Detached leaf assay**

676 To study the effect of genetic variation in host and pathogen on lesion formation,  
677 we infected detached leaves of 12 diverse tomato varieties with the above 97 *B. cinerea*  
678 isolates. We used a randomized complete block design for a total of 6 replicates across  
679 2 experiments. In each experiment, this included a total of 10 plants per genotype  
680 randomized in 12 flats in 3 growth chambers. Each growth chamber block corresponded  
681 with a replicate of the detached leaf assay, such that growth chamber and replicate  
682 shared the same environmental block. At 6 weeks of age, we selected 5 leaves per  
683 plant (expanded leaves from second true leaf or younger), and 2 leaflet pairs per leaf.  
684 We randomized the order of leaves from each plant, and the leaflets were placed on 1%  
685 phytoagar in planting flats, with humidity domes. Our inoculation protocol followed

686 previously described methods (Denby, Kumar et al. 2004, Kliebenstein, Rowe et al.  
687 2005). Spores were collected from mature *B. cinerea* cultures grown on canned peach  
688 plates and diluted to 10 spores/ µL in filter-sterilized 50% organic grape juice. Spores in  
689 grape juice were maintained in 4°C refrigeration or on ice from the time of collection, to  
690 inhibit germination prior to inoculation. The diluted spore suspensions were  
691 homogenized by agitation continuously during the entire process of applying the spores  
692 to all samples. This maintains the spores in the suspension and ensures even  
693 application across samples, then 4µL droplets were placed onto the detached leaflets at  
694 room temperature. The entire inoculation took approximately 2 hour of time per  
695 experiment. Mock-inoculated control leaves were treated with 4µL of 50% organic grape  
696 juice without spores. Digital photos were taken of all leaflets at 24, 48, and 72 hours  
697 post inoculation and automated image analysis was used to measure lesion size.

698

#### 699 **Automated Image Analysis**

700 Lesion area was digitally measured using the EBImage and CRIImage packages  
701 (Pau, Fuchs et al. 2010, Failmezger, Yuan et al. 2012) in the R statistical environment  
702 (R Development Core Team 2008), as previously described (Corwin, Copeland et al.  
703 2016, Corwin, Subedy et al. 2016). Leaflets were identified as objects with green hue,  
704 and lesions were identified as low-saturation objects within leaves. Images masks were  
705 generated for both the leaf and lesion, then manually refined by a technician to ensure  
706 accurate object calling. The area of these leaves and lesions were then automatically  
707 measured as pixels per lesion and converted to area using a 1 cm reference within each  
708 image.

709

#### 710 **Data analysis**

711 We analyzed lesion areas using a general linear model for the full experiment,  
712 including the fixed effects of isolate genotype, plant domestication (*S. lycopersicum* or  
713 *S. pimpinellifolium*), plant genotype (which is nested within domestication status),  
714 experiment, and block (nested within experiment) on lesion area, as well as their  
715 interactions (R lme4 package; (Bates, Maechler et al. 2015)). Two of our 97 isolates that  
716 did not have replication across 2 experiments were dropped at this stage of analysis.

717 The significance of individual terms in the model did not change if experiment and block  
718 were treated as random effects. Adding terms for individual plant, leaf, and leaflet  
719 position did not significantly improve the full model, so they were omitted from further  
720 analysis. This model was used to calculate the significance of each factor and to obtain  
721 the least-squared means of lesion size for each *B. cinerea* isolate x tomato accession  
722 as well as for each *B. cinerea* isolate x domestic/wild tomato. We also calculated a  
723 domestication sensitivity phenotype, Sensitivity = (Domesticated lesion size – Wild  
724 lesion size) / Domesticated lesion size.

725 Using tomato sequence data from the SolCAP diversity panel that contained 9 of  
726 our 12 accessions, we determined pairwise genetic distances (Sim, Durstewitz et al.  
727 2012). We calculated pairwise Euclidean distances between 426 wild and domesticated  
728 tomato accessions from Infinium SNP genotyping at 7,720 loci using the R adegenet  
729 package (Jombart , Sim, Durstewitz et al. 2012). Clustering is by R hclust (in the stats  
730 package) default UPGMA method (R Development Core Team 2008).

731 We used several methods to examine host specialization to tomato within *B.*  
732 *cinerea*. First, we split our *B. cinerea* population into isolates collected from tomato  
733 tissue vs. other hosts. We compared these groups by t-test for virulence on  
734 domesticated tomato genotypes, wild tomato genotypes, or all tomato genotypes. Next,  
735 we used a Wilcoxon signed-rank test to compare the rank order distribution of lesion  
736 sizes across paired tomato genotypes. To examine host specialization to tomato  
737 domestication within *B. cinerea*, we used a Wilcoxon signed-rank test to compare the  
738 rank order of lesion sizes across all domesticated vs. all wild tomato genotypes. Finally,  
739 we conducted single-isolate ANOVAs with FDR correction to identify isolates with a  
740 significant response to plant genotype or domestication status.

741 The model means and Domestication Sensitivity were used as the phenotypic  
742 input for GWA using bigRR, a heteroskedastic ridge regression method that  
743 incorporates SNP-specific shrinkage (Shen, Alam et al. 2013). This approach has  
744 previously had a high validation rate (Ober, Huang et al. 2015, Corwin, Copeland et al.  
745 2016, Francisco, Joseph et al. 2016, Kooke, Kruijer et al. 2016). The *B. cinerea* bigRR  
746 GWA used 272,672 SNPs at MAF 0.20 or greater and <10% missing SNP calls as  
747 described above. Because bigRR provides an estimated effect size, but not a p-value,

748 significance was estimated using 1000 permutations to determine effect significance at  
749 95%, 99%, and 99.9% thresholds (Doerge and Churchill 1996, Shen, Alam et al. 2013,  
750 Corwin, Copeland et al. 2016). SNPs were annotated by custom R scripts with gene  
751 transfer format file construction from the T4 gene models for genomic DNA by linking  
752 the SNP to genes within a 2kbp window (<http://www.broadinstitute.org>, (Staats and van  
753 Kan 2012)). Functional annotations are based on the T4 gene models for genomic DNA  
754 (<http://www.broadinstitute.org>, *B. cinerea*; (Staats and van Kan 2012)). Additional genes  
755 of interest, based on a broad literature search of known virulence loci, were taken from  
756 NCBI (<https://www.ncbi.nlm.nih.gov/>) and included by mapping sequence to the T4  
757 reference using MUMmer v3.0 (Kurtz, Phillippy et al. 2004).

758 To predict expected overlap of significant SNPs across plant genotypes, we used  
759 the average number of significant SNPs per each of the 12 plant genotypes (14,000  
760 SNPs) and calculated expected overlap between those 12 lists using binomial  
761 coefficients. The *B. cinerea* GEMMA used 237,878 SNPs at MAF 0.20 or greater, and  
762 less than 10% missing SNP calls as described above. To determine significance of  
763 SNPs by GEMMA, we used 1000 permutations to determine p-value significance at the  
764 99%, and 99.9% thresholds (Doerge and Churchill 1996, Shen, Alam et al. 2013,  
765 Corwin, Copeland et al. 2016). SNPs were annotated using a custom R script linking the  
766 SNP to genes within a 2kbp window from the gene transfer format file construction from  
767 the B05.10 gene models for genomic DNA (Staats and van Kan 2012, Zerbino,  
768 Achuthan et al. 2017). A table of gene name translations across genome annotations  
769 was pulled from the gene overlap between the bigRR T4 annotation and GEMMA  
770 B05.10 annotation using a custom R script and gene name translations pulled from the  
771 INRA *Botrytis cinerea* Portal (Choquer, Fournier et al. 2007, Viaud, Adam-Blondon et al.  
772 2012). Functional annotations of the overlap lists are based on the T4 gene models for  
773 genomic DNA (<http://www.broadinstitute.org>, *B. cinerea*; (Staats and van Kan 2012)).  
774

## 775 **Supplemental Data Files**

776 Supplemental Data Set 1. Mean of *B. cinerea* lesion size of all isolates across all tomato  
777 accessions.

778 Supplemental Data Set 2. Gene and Function Annotation from B05.10 and T4 GWA  
779 Results  
780 Supplemental Figure 1. Genetic distance between selected tomato accessions.  
781 Supplemental Figure 2. Rank order plot of *B. cinerea* lesion size on two tomato  
782 genotypes.  
783 Supplemental Figure 3. GWA by GEMMA of *B. cinerea* lesion size on individual tomato  
784 genotypes.  
785 Supplemental Figure 4. Frequency of overlap in *B. cinerea* GEMMA GWA significance  
786 across tomato accessions.  
787 Supplemental Figure 5. GEMMA GWA analysis of domestication sensitivity in *B.*  
788 *cinerea*.

789

790

## 791 Figure Legends

792  
793 **Figure 1. *Botrytis cinerea* x tomato diversity in detached leaf assay and digital**  
794 **image analysis.** a) Individual tomato leaflets of 6 *S. lycopersicum* genotypes and 6 *S.*  
795 *pimpinellifolium* genotypes are in randomized rows, spore droplets of individual *B.*  
796 *cinerea* isolates are in randomized columns. Digital images are collected 72 hours post  
797 inoculation. Single droplets of 40 *B. cinerea* spores are infected on randomized leaflets  
798 using randomized isolates, and digital images are taken 72 hours post inoculation.  
799 b) Digital masking of leaf and lesion is followed by automated measurement of area for  
800 each lesion.  
801 c-h) Variation in lesion size resulting of the interaction of *B. cinerea* and diverse tomato  
802 genotypes.  
803 c) Average lesion size of single *B. cinerea* isolates (line traces) across tomato host  
804 genotypes grouped by domestication status.  
805 d) Highlight of the common reference *B. cinerea* isolate B05.10.  
806 e) Highlight of the ten highest-virulence isolates, as estimated by mean virulence across  
807 all tomato genotypes.  
808 f) Highlight of the ten most saprophytic, or low virulence, isolates, as estimated by mean  
809 virulence across all genotypes.  
810 g) Highlight of the five isolates collected from tomato tissue.  
811 h) Highlight of the two isolates with significant domestication sensitivity.

812

## 813 **Figure 2. Distribution of tomato genotype susceptibility to infection with 97** 814 **genetically diverse *B. cinerea* isolates.**

815 Violin plots show the distribution of lesion size caused by *B. cinerea* isolates on each  
816 tomato host genotype. Individual points are mean lesion size for each of the 97 different  
817 isolate-host pairs. The boxes show the 75th percentile distribution, and the horizontal

818 line shows the mean resistance of the specific host genotype. The tomato genotypes  
819 are grouped based on their status as wild or domesticated germplasm.  
820

821 **Figure 3. Distribution of *B. cinerea* virulence by tomato domestication status.**  
822 The violin plots show the mean virulence of each *B. cinerea* isolate on the tomato  
823 genotypes, grouped as wild or domesticated germplasm. The domestication effect on  
824 lesion size is significant (Table 1 ANOVA, p<2e-16). The interaction plot between the  
825 two violin plots connects the average lesion size of a single *B. cinerea* isolate between  
826 the wild and domesticated germplasm.  
827

828 **Figure 4. GWA of *B. cinerea* lesion size on individual tomato genotypes.**  
829 Botrytis cinerea chromosomes are differentiated by shading, alternating light and dark  
830 grey.  
831 a) Manhattan plot of estimated SNP effect sizes from bigRR for *B. cinerea* lesion size  
832 using a single tomato accession, LA2093. Permutation-derived thresholds are shown in  
833 horizontal dashed lines.  
834 b) The number of tomato accessions for which a *B. cinerea* SNP was significantly linked  
835 to lesion development by bigRR using the 99% permutation threshold. Frequency is  
836 number of phenotypes in which the SNP exceeds the threshold. Vertical dotted lines  
837 identify regions with overlap between the top 100 large-effect SNPs for LA2093 and  
838 significance across the majority ( $\geq 6$ ) of tomato genotypes tested.  
839

840 **Figure 5. Frequency of overlap in *B. cinerea* GWA significance across tomato  
841 accessions.**

842 a) The frequency with which the *B. cinerea* SNPs significantly associate with lesion size  
843 on the 12 tomato accessions using bigRR and the 99% permutation threshold. The  
844 black line indicates the expected frequency of random overlap, given the number of  
845 significant SNPs per plant genotype and size of total SNP set. The inset zooms in on  
846 the distribution for overlapping SNPs above 6 plant genotypes for easier visualization.  
847 There were no SNPs expected to overlap by random chance in the inset.  
848 b) The frequency with which *B. cinerea* genes significantly associated with lesion size  
849 on the 12 tomato accessions. Genes were called as significant if there was one  
850 significant SNP called at the 99% permutation threshold within the gene body, or within  
851 2kb of the gene body.  
852

853 **Figure 6. Host specificity of significant SNPs linked to the gene BcT4\_6001  
854 (Bcin14g00870).**

855 a) SNPs with effects estimates above the 99% permutation threshold are colored by  
856 trait (plant phenotype in which the effect was estimated). BcT4\_6001 (Bcin14g00870) is  
857 a pectinesterase gene linked to at least one significant SNP on all 12 of the tested  
858 tomato accessions by bigRR. The annotated exons are depicted as turquoise  
859 rectangles, with the start codon marked with an arrow indicating the direction of  
860 transcription. Red rectangles indicate corresponding linkage disequilibrium blocks from  
861 Figure 6b.  
862 b) Linkage disequilibrium plot, including all pairwise comparisons of SNPs in the 2kb  
863 region surrounding Bcin14g00870. The color scheme for each SNP pair is D'/LOD:

864 white if LOD <2 and D' <1, bright red for LOD ≥2 and D'=1, intermediate shades for  
865 LOD≥2 and D'<1.

866

867 **Figure 7. GWA analysis of domestication sensitivity in *B. cinerea*.**

868 Domestication sensitivity of each isolate was estimated using the average virulence on  
869 the wild and domesticated tomato germplasm and using calculated Sensitivity. This was  
870 then utilized for GWA mapping by bigRR.

871 a) The top 1000 SNPs that significantly affect lesion size across domesticated tomato,  
872 wild tomato or domestication sensitivity are shown. Significance is called as crossing  
873 the 99% permutation threshold.

874 b) Venn diagram of overlapping SNPs identified as crossing the 99% permutation  
875 threshold for each trait.

876 c) Venn diagram of overlapping genes identified as crossing the 99% permutation  
877 threshold for each trait. Genes were called as significant if there was one significant  
878 SNP within the gene body or within 2kb of the gene body.

879

880

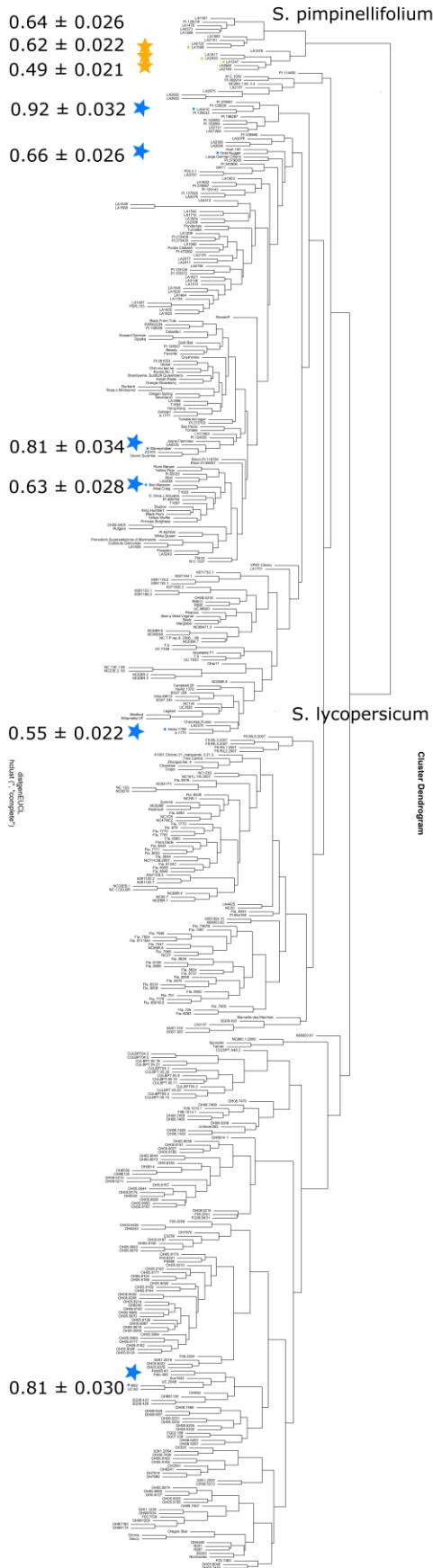
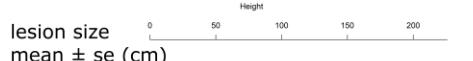
See separate .xls file

**Supplemental Data Set 1. Mean of *B. cinerea* lesion size of all isolates across all tomato accessions.**

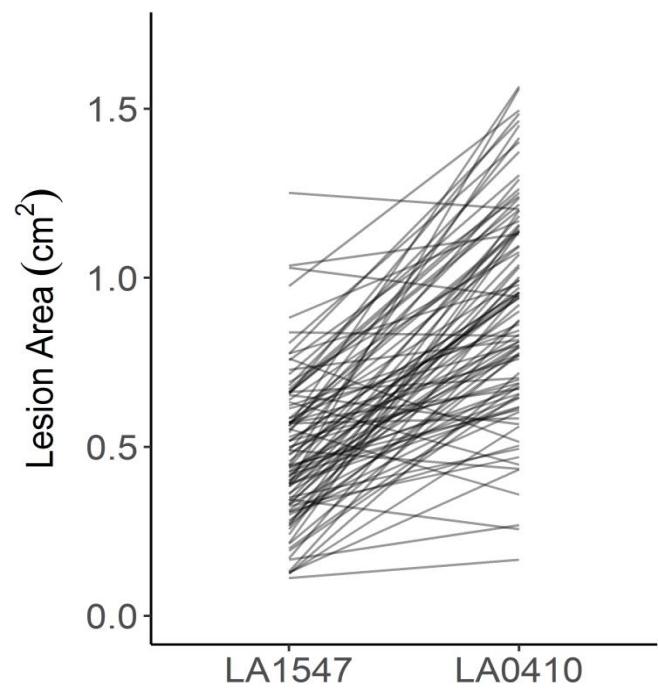
See separate .xls file

## **Supplemental Data Set 2. Gene and Function Annotation from B05.10 and T4 GWA Results**

- a) Genes with significant SNPs on at least two tomato accessions by both bigRR on T4 and GEMMA on B05.10.
- b) Genes with significant SNPs linked to Botrytis virulence response to tomato domestication by both bigRR on T4 and GEMMA on B05.10.
- c) Functional categories significantly overrepresented in genes linked to Botrytis virulence response to tomato by both bigRR on T4 and GEMMA on B05.10.
- d) Functional categories significantly overrepresented in genes linked to Botrytis virulence response to tomato domestication by both bigRR on T4 and GEMMA on B05.10.
- e) Genes with significant SNPs from bigRR on T4 for Botrytis virulence in 11 or 12 of the tomato accessions.
- f) Functional categories significantly overrepresented in genes linked to Botrytis virulence response to tomato domestication by bigRR on T4 alone.

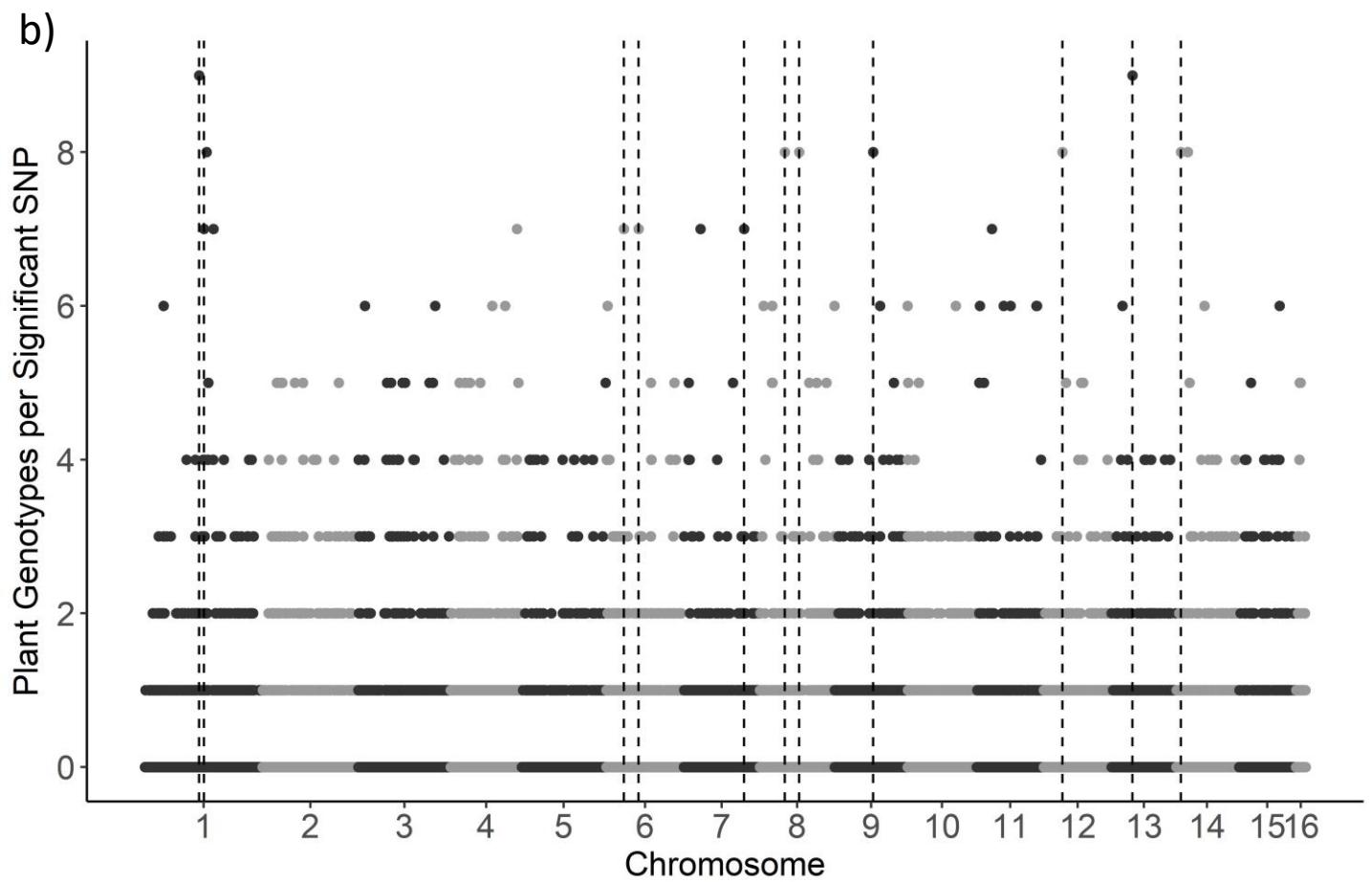
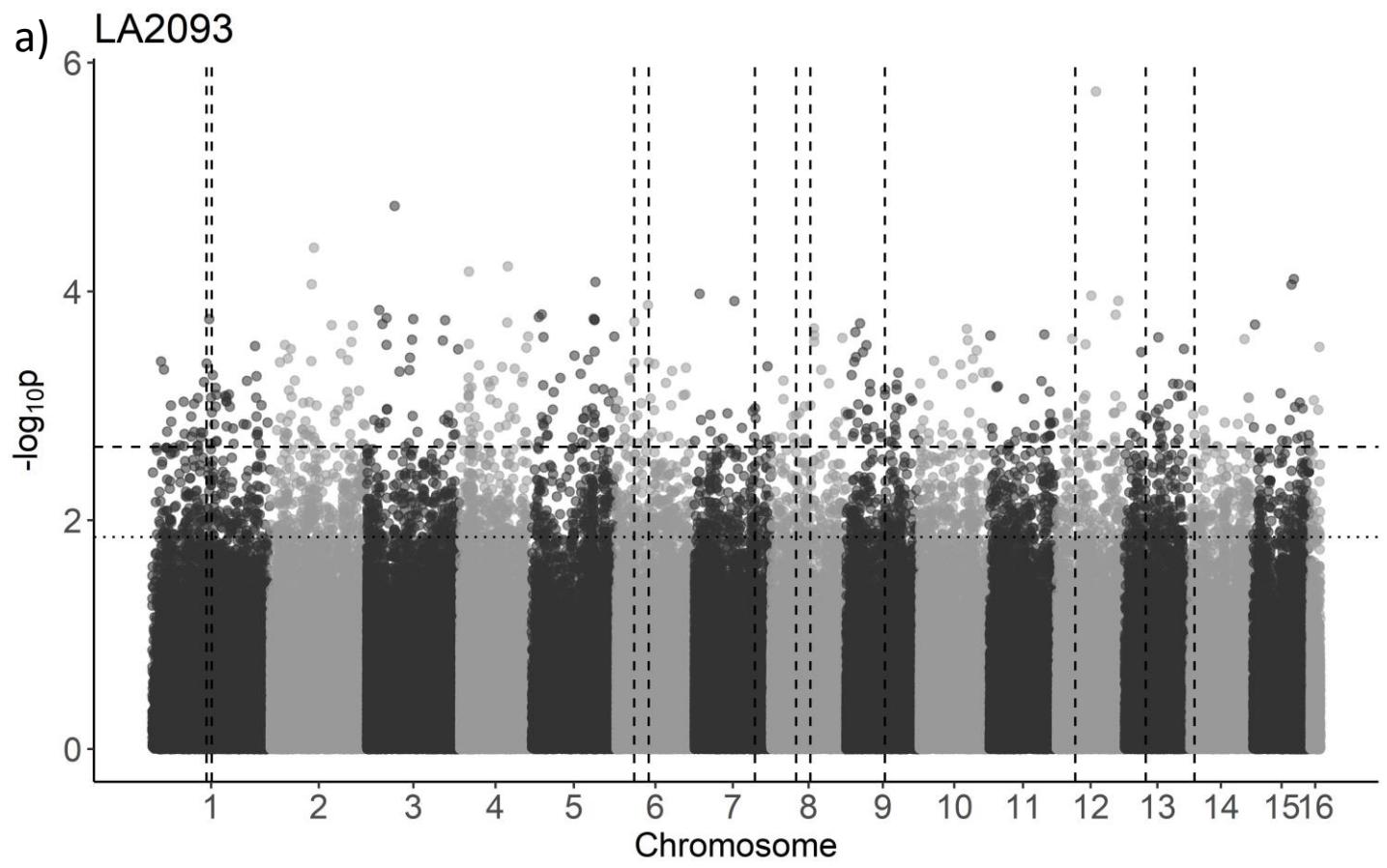


**Supplemental Figure 1. Genetic distance between selected tomato accessions.** Pairwise Euclidean distances between 426 wild and domesticated tomato accessions in the SolCAP diversity panel calculated from Infinium SNP genotyping at 7,720 loci (Sim 2012). Clustering is by R hclust's default UPGMA method. *S. pimpinellifolium* accessions in the current study are marked with orange stars, *S. lycopersicum* accessions in the current study are marked with blue stars. All of the wild *S. pimpinellifolium* included in this panel cluster with our 3 accessions. Mean  $\pm$  SE of lesion size of *B. cinerea* across the full study is included for each accession.



**Supplemental Figure 2. Rank order plot of *B. cinerea* lesion size on two tomato genotypes.**

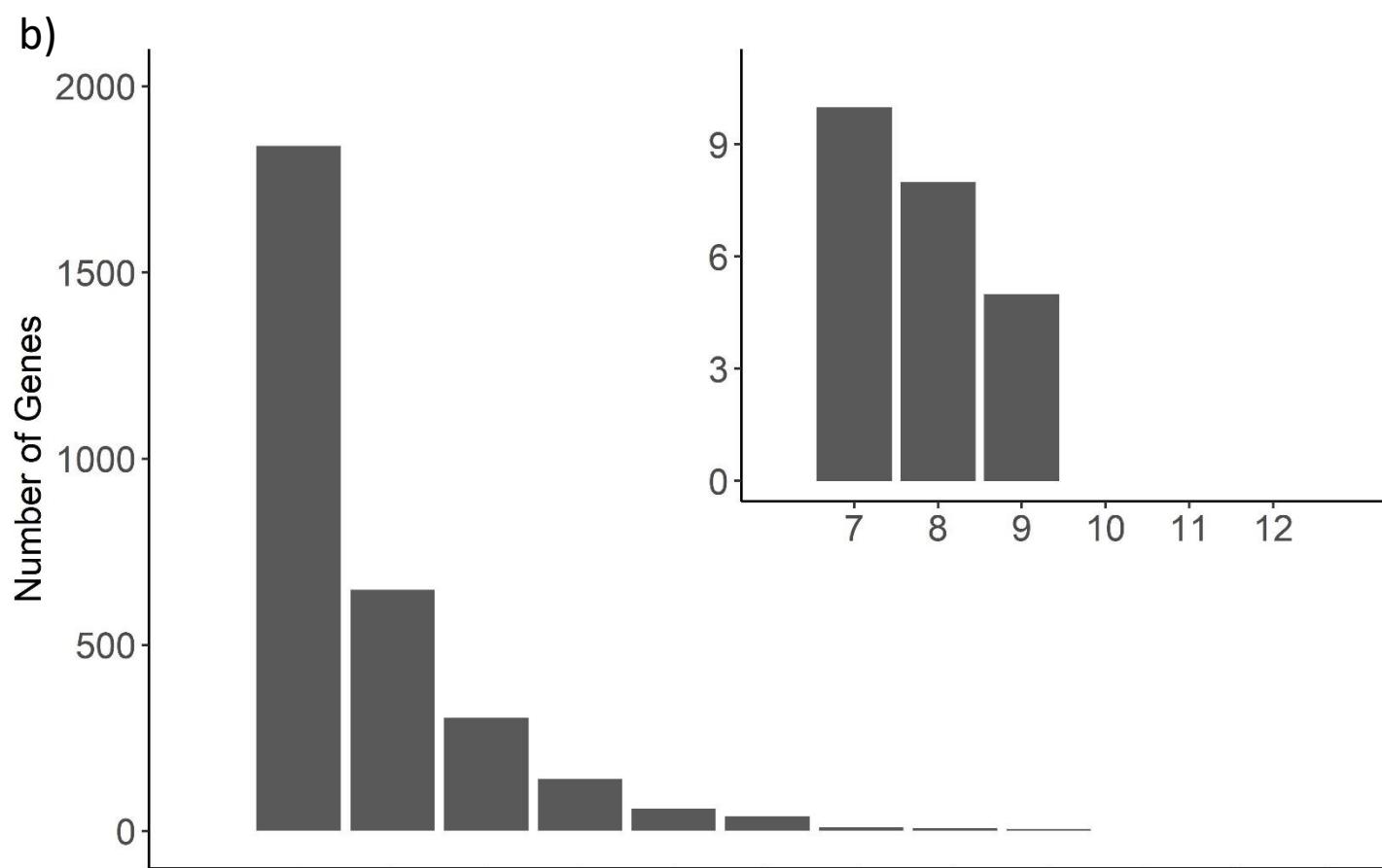
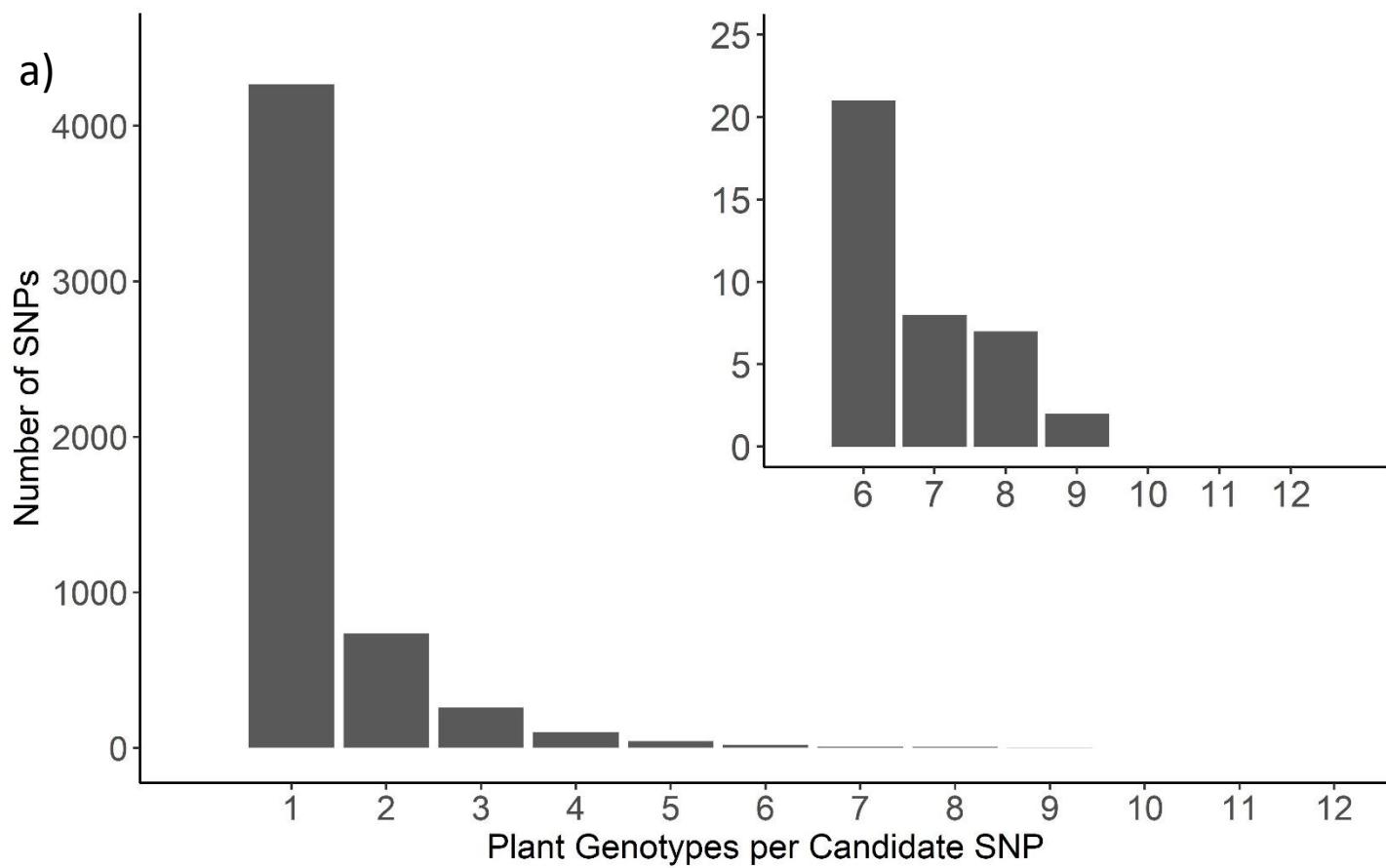
Each *B. cinerea* isolate is a straight line tracing mean lesion size on LA1547 to mean on LA0410, the two host genotypes with the most pronounced effect on the rank order of isolates by lesion size (Wilcoxon signed-rank test with FDR-correction,  $p < 7.18e-17$ , Table S1).



**Supplemental Figure 3. GWA by GEMMA of *B. cinerea* lesion size on individual tomato genotypes.**

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

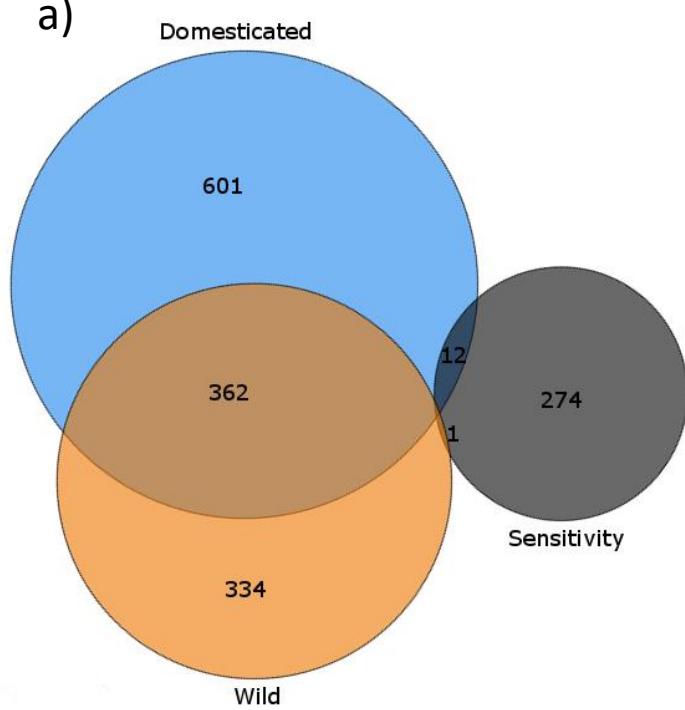
- a) Manhattan plot of estimated SNP effect sizes for *B. cinerea* lesion size using a single tomato accession, LA2093. The 99% permutation threshold for SNP significance is shown with a dotted line, the 99.9% threshold is a dashed line.
- b) The number of tomato accessions for which a *B. cinerea* SNP was significantly linked to lesion development using the 99.9% permutation threshold. Frequency is number of phenotypes in which the SNP is significant. Vertical dotted lines identify regions with overlap between the significant SNPs for LA2093 and significance across most ( $\geq 10$ ) of tomato genotypes tested.



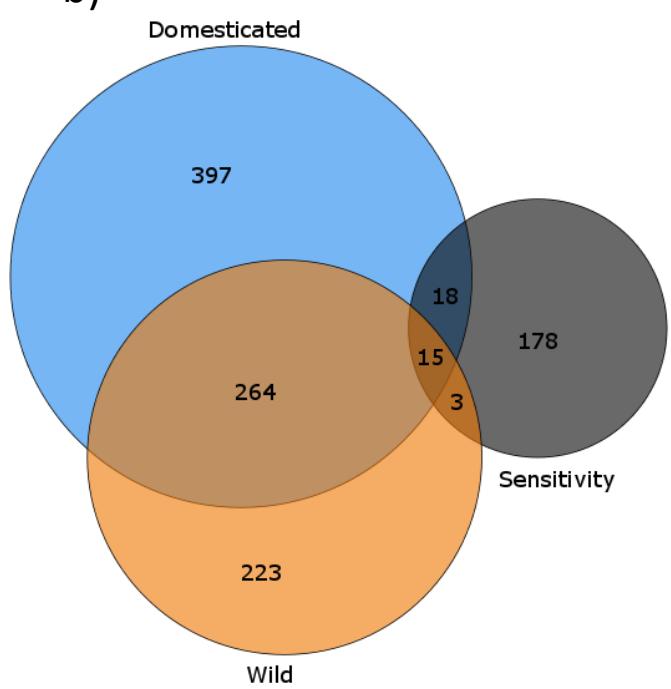
**Supplemental Figure 4. Frequency  
of overlap in *B. cinerea* GEMMA  
GWA significance across tomato  
accessions.**

- a) Frequency with which the top 1000 *B. cinerea* SNPs per phenotype significantly associated with lesion size on the 12 tomato accessions using the 99.9% permutation threshold.
- b) Frequency with which a *B. cinerea* gene significantly associated with lesion size on the 12 tomato accessions. Genes were called as significant if there was one of the top 1000 significant SNPs per phenotype at the 99.9% permutation threshold within the gene body, or within 2kb of the gene body.

a)



b)



## **Supplemental Figure 5. GEMMA GWA analysis of domestication sensitivity in *B. cinerea*.**

Domestication sensitivity of each isolate was estimated using the average virulence on the wild and domesticated tomato germplasm and using calculated Sensitivity. This was then utilized for GWA mapping by GEMMA.

- a) Venn diagram of overlapping SNPs identified as crossing the 99.9% permutation threshold for each trait.
- b) Venn diagram of overlapping genes identified as crossing the 99.9% permutation threshold for each trait. Genes were called as significant if there was one significant SNP within the gene body or within 2kb of the gene body.

**Table S1. Mean of *B. cinerea* lesion size of all isolates**

Wild								Domesticated
	LA0480	LA1547	LA1589	LA1684	LA2093	LA2176	LA0410	LA2706
1.01.01	0.489	0.308	0.700	0.282	0.399	0.594	0.504	0.476
1.01.02	0.753	0.656	0.454	0.626	0.792	0.894	1.485	0.357
1.01.03	1.066	0.437	1.057	0.279	0.889	0.345	0.772	0.864
1.01.04	0.606	0.446	0.182	0.881	0.915	1.095	0.610	0.631
1.01.06	0.666	0.550	0.881	0.587	0.861	0.911	1.093	0.762
1.01.15	0.500	0.569	0.577	0.558	0.675	1.009	1.138	0.627
1.02.01	0.962	0.840	1.004	0.463	0.625	1.060	0.828	1.337
1.02.02	0.436	0.728	0.504	0.359	0.744	0.574	0.816	0.505
1.02.03	0.782	0.131	0.753	0.768	0.525	0.614	0.876	1.071
1.02.04	0.728	0.170	0.762	0.242	0.479	0.930	0.959	0.915
1.02.05	0.524	0.614	0.652	0.993	0.641	0.869	0.801	1.092
1.02.06	0.398	0.166	0.372	0.250	0.365	0.068	0.269	0.664
1.02.15	0.911	0.490	0.287	0.492	0.619	0.394	0.434	0.680
1.02.16	0.648	0.561	0.588	0.119	0.507	1.010	1.237	0.844
1.02.17	0.649	0.282	0.575	0.228	0.681	0.466	0.771	0.803
1.02.18	0.428	0.308	0.357	0.523	0.545	0.497	0.645	0.225
1.02.20	1.036	0.574	0.457	0.632	0.493	0.568	0.760	0.900
1.03.02	0.501	0.516	0.525	0.962	0.609	0.738	0.956	0.621
1.03.04	0.475	0.756	0.815	0.340	0.750	0.694	1.241	0.839
1.03.12	0.693	0.543	1.055	0.757	0.935	1.062	1.414	0.914
1.03.16	0.422	0.671	0.425	0.594	0.805	0.992	1.264	1.096
1.03.18	0.838	0.383	0.679	0.917	0.807	0.464	0.801	0.521
1.03.19	0.367	0.441	0.320	0.335	0.491	0.553	0.657	0.276
1.03.20	0.359	0.569	0.372	0.595	0.304	0.314	0.584	0.501
1.03.22	0.446	0.351	0.448	0.445	0.437	0.433	0.494	0.509
1.03.23	0.744	0.500	0.814	0.472	0.739	0.892	0.699	0.602
1.04.01	0.719	0.571	0.494	1.090	0.609	0.918	0.992	0.486
1.04.02	0.433	0.390	0.393	0.267	0.427	0.856	0.616	0.646
1.04.03	0.559	0.518	0.553	0.396	0.590	0.778	0.957	0.491
1.04.04	0.192	0.270	0.366	0.491	0.389	0.649	0.795	0.597
1.04.05	0.310	0.216	0.438	0.330	0.359	0.662	1.138	0.817
1.04.12	0.350	0.553	0.288	0.448	0.190	0.723	0.359	0.171
1.04.15	0.765	0.256	0.306	0.342	0.633	0.628	1.003	0.337
1.04.17	0.545	0.341	0.654	0.911	0.534	0.596	1.039	0.705
1.04.19	0.801	0.394	0.534	0.359	0.507	0.544	0.833	0.270
1.04.20	0.655	0.401	0.403	0.436	0.632	0.645	0.812	0.742
1.04.21	0.397	0.632	0.539	0.443	0.558	0.828	0.447	0.464
1.04.25	0.470	0.622	0.417	0.467	0.425	0.431	0.844	0.963
1.05.04	0.599	0.265	0.522	0.774	0.386	0.652	1.198	0.649
1.05.11	0.423	0.426	0.661	0.241	0.379	0.537	0.901	0.573
1.05.14	0.576	0.518	0.405	1.445	0.369	0.776	0.689	0.708
1.05.16	0.694	0.275	0.453	0.154	0.350	0.643	1.032	0.600
1.05.17	0.644	0.639	0.958	0.956	0.571	0.986	1.095	0.581
1.05.22	0.564	0.213	0.805	0.240	0.390	0.316	0.778	0.404

1.05.24	0.279	0.324	0.238	0.100	0.346	0.494	0.470	0.429
2.04.03	0.368	0.458	0.596	0.754	0.490	0.455	0.952	0.480
2.04.04	1.119	1.036	1.013	0.720	0.673	0.978	1.130	1.066
2.04.08	1.409	0.777	0.980	0.726	0.731	0.727	0.979	1.192
2.04.09	0.730	0.328	0.910	0.813	0.900	0.848	0.995	1.362
2.04.11	0.662	0.976	0.658	0.762	0.639	0.905	1.495	1.199
2.04.12	1.311	0.807	1.436	1.104	0.605	0.865	1.402	1.621
2.04.14	0.820	0.441	0.180	0.506	0.643	0.694	1.158	0.771
2.04.17	0.581	0.390	0.563	0.523	0.560	0.931	1.561	1.159
2.04.18	0.797	0.682	0.756	0.850	1.254	0.772	1.373	1.224
2.04.20	1.167	0.333	0.918	0.642	0.692	0.738	0.920	1.301
2.04.21	0.546	0.662	0.774	0.533	0.402	0.853	0.703	1.037
2004	0.474	0.391	0.507	0.509	0.689	0.623	0.647	0.954
94.4	0.571	0.572	0.433	0.618	0.525	1.238	0.672	0.861
Acacia	0.465	0.529	0.662	0.181	0.599	1.034	0.773	0.894
Apple 404	0.372	0.585	0.762	0.762	0.681	0.534	0.863	1.020
Apple 517	0.802	1.251	0.690	1.256	0.897	0.478	1.203	0.876
Ausubel	0.910	0.775	0.986	0.724	0.876	0.735	1.465	1.448
B05.10	0.729	0.312	0.971	0.449	0.531	0.726	0.872	0.690
BMM	0.665	0.358	0.948	1.061	0.644	1.031	1.069	0.854
BPA1	0.465	0.418	0.586	0.689	0.882	0.610	0.619	0.900
Davis Navel	0.655	0.497	0.475	0.343	0.645	0.796	0.812	0.777
Esparato Fresca	0.311	0.299	0.202	0.485	0.226	0.383	0.604	0.284
Fd1	0.873	0.363	0.884	0.820	0.803	1.068	0.796	1.069
Fd2	0.666	0.398	0.468	0.587	0.624	1.134	0.971	1.415
Fresa 525	0.673	0.446	0.962	0.481	1.011	1.343	1.450	1.123
Fresa SD	0.730	0.192	0.453	0.278	0.664	0.757	0.655	0.451
Gallo 1	0.378	0.329	0.463	0.477	0.352	0.450	0.688	0.375
Gallo 2	0.475	0.129	0.684	0.053	0.591	0.297	0.433	0.506
Geranium	0.802	0.479	0.666	0.563	0.507	1.083	0.941	0.950
Grape	0.582	0.241	0.843	0.709	0.615	0.641	1.154	0.877
Katie Tomato	0.705	1.030	0.860	1.004	0.751	0.663	0.943	1.628
Kern A2	1.709	0.882	0.943	0.747	0.975	0.848	1.168	1.293
Kern B1	0.860	0.409	0.533	0.620	0.863	1.424	1.183	1.089
Kern B2	1.132	0.715	1.155	0.656	0.762	1.243	1.303	1.069
KGB1	0.322	0.426	0.171	0.211	0.342	0.217	0.675	0.288
KGB2	0.769	0.476	1.197	0.535	0.800	1.053	0.940	0.763
MEAP6G	0.513	0.382	0.725	0.087	0.624	0.339	1.138	0.972
Mex 03	0.588	0.414	0.573	0.833	0.520	1.103	0.948	1.013
Molly	0.524	0.653	0.301	0.668	0.651	0.605	0.567	0.662
Navel	0.149	0.112	0.074	0.193	0.195	0.107	0.167	0.137
Noble Rot	0.203	0.125	0.165	0.358	0.131	0.275	0.719	0.186
Peachy	0.440	0.345	0.397	0.269	0.586	0.870	0.256	0.639
Pepper	0.594	0.660	0.571	0.692	0.661	1.216	1.202	0.447
Pepper Sub	0.589	0.584	0.802	0.606	0.706	0.897	1.143	1.130
Philo Menlo	1.158	0.662	1.250	1.016	0.993	1.543	1.252	1.494
Rasp	0.794	0.563	0.718	0.810	0.876	1.127	1.567	0.914

Rose	0.200	0.200	0.072	0.108	0.208	0.385	0.681	0.429
Supersteak	0.815	0.691	0.769	0.510	0.855	1.146	1.076	0.854
Triple 3	0.948	0.659	1.295	1.156	1.150	0.893	1.217	1.190
UK Razz	0.907	0.489	1.072	0.548	0.761	1.191	1.291	1.660

## olates across all tomato accessions.

LA3008	LA3475	LA4345	LA4355
0.505	0.677	0.780	0.860
0.583	1.144	0.354	0.397
1.090	1.217	0.700	0.582
1.151	1.259	0.765	0.586
0.910	0.940	0.647	0.510
0.336	0.941	0.135	0.582
0.839	1.587	0.573	0.611
0.380	0.514	0.531	0.384
0.578	0.694	0.747	0.575
0.305	0.695	0.712	0.732
0.494	0.817	0.692	0.590
0.369	1.026	0.531	0.373
0.663	0.545	0.401	0.315
0.894	0.586	0.511	0.639
0.493	0.642	0.274	0.308
0.299	0.802	0.239	0.513
0.534	0.936	0.472	0.590
0.375	0.752	0.495	0.656
0.625	0.966	0.499	0.850
0.620	0.963	0.552	0.878
0.641	0.643	0.662	1.031
0.868	1.542	0.285	0.571
0.342	0.624	0.243	0.199
0.928	0.961	0.660	0.683
0.619	0.369	0.294	0.589
0.709	0.631	0.606	0.833
0.591	1.024	0.543	0.527
0.196	0.695	0.336	0.911
0.417	0.954	0.531	0.669
0.573	0.574	0.361	0.329
0.360	0.530	0.261	0.260
0.596	0.519	0.240	0.177
0.198	0.231	0.256	0.183
0.315	0.737	0.442	0.641
0.339	0.828	0.443	0.409
0.517	0.711	0.576	0.497
0.576	0.777	0.458	0.576
0.887	1.109	0.448	0.937
0.201	0.359	0.238	0.258
0.334	0.581	0.369	0.414
0.374	0.889	0.595	0.469
0.551	0.371	0.546	0.494
1.238	0.754	0.460	0.593
0.880	0.505	0.462	0.441

0.337	0.509	0.463	0.278
0.533	0.674	0.539	0.785
1.328	1.547	0.775	0.695
1.448	1.085	0.785	1.049
0.831	0.701	0.537	1.088
1.121	0.994	0.802	0.820
1.194	1.428	1.047	1.108
0.483	0.531	0.620	0.948
0.773	0.625	0.562	0.676
0.970	1.190	0.774	1.305
0.373	0.797	0.530	0.758
0.515	0.680	0.660	0.860
0.437	1.045	0.587	0.443
0.491	1.174	0.583	0.666
0.721	0.415	0.527	1.044
0.964	0.791	0.636	0.725
0.808	0.980	0.689	1.024
1.105	1.110	0.517	0.861
0.458	0.999	0.414	0.909
0.493	0.866	0.531	0.607
0.577	0.831	0.515	0.617
0.606	0.269	0.538	0.608
0.246	0.196	0.287	0.360
0.696	0.678	0.548	0.494
1.691	1.390	1.457	0.820
0.602	0.669	0.758	1.427
0.707	0.913	0.394	0.428
0.344	0.525	0.297	0.391
0.198	0.863	0.336	0.292
0.765	1.418	0.652	0.679
0.512	0.741	0.501	0.695
1.131	1.058	0.733	0.919
0.881	1.437	1.135	1.170
0.830	1.122	0.906	0.983
0.656	1.160	0.945	1.024
0.468	0.548	0.272	0.333
0.363	1.047	0.562	0.936
0.407	0.535	0.777	0.955
0.194	0.728	0.450	0.435
0.556	0.788	0.523	0.733
0.339	0.299	0.137	0.053
0.123	0.211	0.113	0.172
0.163	0.448	0.268	0.397
0.643	0.464	0.516	0.524
0.374	0.931	0.732	0.814
0.952	0.972	0.691	0.836
0.752	0.909	0.751	0.714

0.654	0.542	0.218	0.569
0.542	0.841	0.895	1.092
1.032	1.106	1.162	1.157
1.111	0.939	0.898	1.208

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