Running title: eGWA of Botrytis-Arabidopsis co-transcriptome

**Pathogen genetic control of transcriptome variation in the *Arabidopsis thaliana* – *Botrytis cinerea* pathosystem**

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**ABSTRACT**

Disease symptoms arise from the interaction of the host and pathogen genomes. However, little is known about how genetic variation in the interaction modulates both organisms’ transcriptomes, especially in complex interactions like those between generalist pathogens and their plant hosts. To begin mapping how polygenic pathogen variation influences both organisms’ transcriptomes, we used the *Botrytis cinerea* - *Arabidopsis thaliana* pathosystem. We measured the co-transcriptome across a genetically diverse collection of 96 *B. cinerea* isolates infected on the Arabidopsis wildtype, Col-0. Using the *B. cinerea* genomic variation, we performed genome-wide association (GWA) for each of 23,947 measurable transcripts in the host, and 9,267 measurable transcripts in the pathogen. Unlike other eGWA studies, there was a relative absence of *cis*-eQTL that is likely explained by structural variants and allelic heterogeneity within the pathogen’s genome. This analysis identified mostly *trans*-eQTL in the pathogen with eQTL hotspots dispersed across the pathogen genome that altered the pathogen’s transcripts, the host’s transcripts, or both the pathogen and the host. Gene membership in the *trans-*eQTL hotspots suggests links to several known and many novel virulence mechanisms in the plant-pathogen interaction. Genes annotated to these hotspots provide potential targets for blocking manipulation of the host response by this ubiquitous generalist pathogen. This shows that genetic control over the co-transcriptome is polygenic, similar to the virulence outcome in the interaction of *Botrytis cinerea* on *Arabidopsis thaliana*.

**INTRODUCTION**

Infectious disease is an interaction between host and pathogen. Its outcome is driven by the genetics of both organisms. The mechanisms of plant-pathogen interactions are often divided into qualitative, in which a few genetic variants of large effect shape binary disease outcomes, or quantitative, in which a spectrum of outcomes arise from the interaction of polygenic variation in the host and pathogen. The past decades have witnessed the unraveling of the molecular basis of large-effect loci on both the host side and the pathogen side that control qualitative interactions (Giraldo and Valent 2013, Marone, Russo et al. 2013, Meng and Zhang 2013, Cui, Tsuda et al. 2015, Lo Presti, Lanver et al. 2015). In this model, alternative alleles of these genes, via differential recognition events surrounding their proteins, create sweeping differences in the transcriptome and phenotypic responses to infection in both the host and pathogen. However, plant-microbe interactions cover a full range of genetic architectures, from few genes of large phenotypic effect to many genes of small effect (Poland, Balint-Kurti et al. 2009, Kou and Wang 2010, Lannou 2012). In contrast to qualitative systems, quantitative plant-pathogen interactions exhibit a lack of virulence/ resistance genes that explain large proportions of the variance in virulence in the population (Poland, Balint-Kurti et al. 2009, Kou and Wang 2010, St. Clair 2010, Roux, Voisin et al. 2014). Rather, the genetic basis of disease progression for both organisms in these interactions is highly polygenic with genetic variation influencing loci that alter a diverse array of molecular mechanisms, extending well beyond perception events (Glazebrook 2005, Nomura, Melotto et al. 2005, Goss and Bergelson 2006, Rowe and Kliebenstein 2008, Barrett, Kniskern et al. 2009, Corwin, Copeland et al. 2016, Bartoli and Roux 2017, Wu, Sakthikumar et al. 2017, Atwell, Corwin et al. 2018, Fordyce, Soltis et al. 2018, Soltis, Atwell et al. 2019). It is, however, unclear how these polygenic molecular systems in different organisms interact to alter higher-order phenotypes such as virulence, or even more direct phenotypes like the transcriptome of both species. There is some conflicting evidence on the balance of the system, with some studies and traits suggesting that genetic variation in the pathogen dominates the system (Bartha, McLaren et al. 2017, Wang, Roux et al. 2018), while others suggest a balanced contribution of plant and pathogen genetics (Corwin, Copeland et al. 2016, Fordyce, Soltis et al. 2018, Soltis, Atwell et al. 2019). Thus, there is a need to develop genomic approaches to understand how polygenic information is transmitted between the pathogen and the host to shift the genomic response of both organisms.

The polygenic variation in the pathogen should influence numerous genes that consequently shift the pathogen’s transcriptome and cause differential expression of various virulence mechanisms. This variation in virulence mechanism will then impact the host and lead to shifts in the host’s resistance-associated transcriptome. Thus, by measuring the transcriptome in both the pathogen and the host, it should be possible to map how genetic variation in the pathogen is conveyed through the pathogen’s transcriptome and concurrently how the host’s transcriptome responds. Recent work has shown that it is possible to measure the pathogen’s transcriptome in planta in *A. thaliana* -*Pseudomonas syringae* leading to new hypothesis about virulence (Nobori, Velásquez et al. 2018). In the *A. thaliana* - *B. cinerea* system, t In this pathosystem,a co-transcriptome study with simultaneous analysis of the host’s and pathogen’s transcripts was recently done through single sample RNA-Seq (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). This co-transcriptome approach allowed mapping of key virulence networks in the pathogen and resistance responses within the host (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). Further, this study revealed a single network of transcripts from both species pathogen and host (Zhang, Corwin et al. 2018). However, these studies did not assess the genetic architecture behind these co-transcriptome interactions.

These connections can be disentangled by utilizing GWA to identify expression quantitative trait loci (eQTL)—SNPs correlated with variation in transcript expression profiles. These SNPs tag polymorphisms that cause the differential transcript accumulation and can be parsed into either *cis* or *trans* effects. Locally acting (*cis*) eQTL indicate regulatory variation within or near the expressed gene itself. *trans*-eQTL indicate SNPs that are acting at a distance and are polymorphisms that affect regulatory processes influencing the expression of the transcript. If a *trans*-eQTL affects many transcripts, it is classified as a hotspot and the SNP may influence a regulatory process that in turn influences a large number of transcripts. eQTL analysis has been utilized to study host-pathogen interactions, albeit with a focus either on host or pathogen. Frequently, these studies focus on the host’s response, such as mapping how host loci control host gene expression over time using either traditional QTL mapping or GWA analysis (Chen, Hackett et al. 2010, Hsu and Smith 2012, Zou, Chai et al. 2012, Allen, Carrasquillo et al. 2016, Christie, Myburg et al. 2017). Additional studies have begun to invert this scheme by looking at how genetic variation in the pathogen influences the host transcriptome to identify pathogen loci modulating host expression levels, and thus to identify candidate loci for interspecific signals (Wu, Cai et al. 2015, Guo, Fudali et al. 2017). These studies show that it is possible to identify pathogen loci that influence host gene expression, but they have thus far addressed pathogen populations with limited genetic variation, and thus identify the few polymorphic loci between strains with strongest effects on transcriptomic variation (Wu, Cai et al. 2015, Guo, Fudali et al. 2017). Expanding these approaches would require conducting a co-transcriptome analysis wherein both the host and pathogen transcriptomes are measured using a natural population of the pathogen, to identify a broader sampling of the pathogen loci affecting expression during infection of the host.

Thus, we conducted a GWA analysis of the pathogen and host transcriptomes to identify loci in *B. cinerea* that may be modulating the outcome of the interaction between the species. We utilized a previous co-transcriptome dataset of variation in individual transcript expression profiles of diverse *B. cinerea* isolates infecting the wildtype host Col-0 *A. thaliana* (Zhang, Corwin et al. 2017, Zhang, Corwin et al. 2018). The genomes of both the host and the pathogen harbor extensive genetic diversity that has been successfully used for GWA to identify loci controlling virulence (Atwell, Corwin et al. 2018, Soltis, Atwell et al. 2019). Further, the virulence outcome of the interaction is easily measured via high-throughput digital imaging and has previously been utilized for studies into the transcriptomic and genomic basis for virulence allowing for a large body of molecular information to underpin any hypothesis generation from GWA (Denby, Kumar et al. 2004, Rowe and Kliebenstein 2008, Zhang, Corwin et al. 2017, Atwell, Corwin et al. 2018, Soltis, Atwell et al. 2019). The loci tagged by these SNPs have an explicit directionality of effect, as genetic causality must arise within the pathogen and then extend to the host. Our analysis found mostly small-effect polymorphisms dispersed throughout the *B. cinerea* genome, with several *trans*-eQTL hotspots. These hotspot loci are linked to specific host or pathogen transcript co-expression modules and to variation in lesion size. There was no identifiable overlap in the hotspots that influenced the host’s or the pathogen’s transcriptome, suggesting a surprisingly independent basis of transcriptional regulation of host and pathogen by the *B. cinerea* genome. Among these hotspot loci, all appeared to tag novel genes not previously identified as controlling plant-pathogen virulence interactions. Overall, we identify a mix of novel loci potentially controlling the interaction of *A. thaliana* and *B. cinerea* via modulation of gene expression, with evidence for connections to virulence.

**RESULTS**

**eQTL indicate polygenic transcriptome modulation**

To better understand how natural genetic variation in the pathogen influences both the host and pathogen transcriptomes, we performed expression GWA across all genes expressed in both species within the *B. cinerea* - *A. thaliana* pathosystem. This incorporated the expression profiles of 9,267 *B. cinerea* genes and 23,947 Col-0 *A. thaliana* genes,each as individual traits across 96 diverse *B. cinerea* isolates. For each trait, we used a Genome-wide Efficient Mixed Model Association (GEMMA) model with a previous *B. cinerea* genome-wide SNP dataset of 237,878 SNPs with a conservative minimum minor allele frequency of 0.20 (Zhou and Stephens 2012, Atwell, Corwin et al. 2018). GEMMA estimates the significance of effects of each SNP on the focal trait as a p-value after accounting for potential effects of population structure within the *B. cinerea* isolates. In total, GEMMA was able to identify *B. cinerea* SNPs linked to transcriptional variation in 5,213 *A. thaliana* genes and 1,616 *B. cinerea* genes (Figure 1). For these genes with significant SNPs, there was a median of 10±25 SNPs per transcript for *B. cinerea*, and a median of 10±13 SNPs per transcript or *A. thaliana* transcripts (Figure S1a, S1b). Filtering the SNP-transcript associations for smallest p-value or largest effect estimate, we detected no *cis-*effect polymorphisms in the top 50 candidates (data not shown). Further, the distribution of p-values for significant SNPs suggest a highly polygenic basis of loci modulating transcriptome variation (Figure S1c, S1d).

Given the scale of this dataset at 33,214 transcripts, it was not viable to estimate empirical significance thresholds for every transcript using 1,000 or more permutations. However, we permuted the whole dataset across each of the tens of thousands of traits five times to break all real phenotype-genotype associations and repeated GEMMA to get a feel for the potential for dominant patterns that may exist randomly (individual expression profiles in *B. cinerea* and *A. thaliana*). We then compared the permuted minimum p-value per transcript across all SNPs to the data obtained from real traits. This showed that the top SNP per trait for most genes show a stronger association in our observed data than across any of the 5 permutations. In *B. cinerea*, the observed p-value is lower for 69% of genes, much more than the expected 17% due to random chance, and in *A. thaliana* the observed p-value is lower for 58% of genes. Thus, to develop genomic summary images of the results, we focused on the top significant SNP per transcript for the remaining analysis.

**Absence of transcriptome cis-effect dominance**

A hallmark of eQTL mapping studies using either GWA or structured mapping populations in a wide range of species is the occurrence of large-effect loci that map to the gene itself, i.e. *cis-*eQTL or *cis*-SNPs (Brem, Yvert et al. 2002, Schadt, Monks et al. 2003, Monks, Leonardson et al. 2004, Keurentjes, Fu et al. 2007, West, Kim et al. 2007, Zou, Chai et al. 2012). To test if the *B. cinerea* transcriptome shows a similar *cis-*eQTL pattern, we plotted the position of the transcript’s genomic position against the top GWA SNP for all the *B. cinerea* transcripts. We first focused on the single top SNP hit per transcript, with the lowest p-value (strongest evidence of significant effect on expression) in the gene of interest. If control of gene expression is localized to the gene itself or toproximate loci, we would expect a strong linear (*cis*-diagonal) association between the center of each gene and the genomic location of its top SNP hit. However, there was no evidence of any cis-diagonal (Figure 2). This pattern held whether we examine the top SNP per transcript (Figure 2a) or the top 10 SNPs per transcript (Figure 2b). In contrast, there was evidence for *trans*-eQTL hotspots; loci which modulate expression variation across many of the pathogen genes (Figure 2).

To test if there might be a bias towards *cis*-effects that may function at a close distance, we calculated the distance between the center of each transcript and the top associated SNP. If *cis*- acting loci contribute the bulk of genetic control of expression variation, we would expect to see a high frequency of short-distance associations, and a rapid decline to a plateau moving away from the gene of interest. However, we observe that distances between transcript center and top SNP as far as 2 Mb are common (Figure S3). These distances are similar to what would happen if the causal SNPs had no *cis-* association and were instead scattered across the genome (Figure S3). As such, we do not see evidence for *cis*-effect loci overrepresented in the top candidates for control of expression variation. Rather, most of the loci that we can associate with potentially influencing gene expression variation in *B. cinerea* on *A. thaliana* is *trans*-acting.

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

The absence of a dominant *cis*- pattern in the genome-wide transcript-to-SNP associations could be caused by a relative absence of *cis-* variation. Alternatively, haplotype heterogeneity or allele frequency may complicate the ability to accurately identify *cis*-polymorphisms (Chan, Rowe et al. 2010, Rivas, Beaudoin et al. 2011, Visscher, Wray et al. 2017). To test between these possibilities, we conducted a more focused analysis on three biosynthetic pathways that exist as gene clusters: the botcinic acid biosynthetic pathway (13 genes, 55.8 kb), botrydial biosynthetic pathway (7 genes, 26 kb), and a putative cyclic peptide pathway (10 genes, 46.5 kb) (Deighton, Muckenschnabel et al. 2001, Colmenares, Aleu et al. 2002, Porquier, Morgant et al. 2016, Zhang, Corwin et al. 2018). These pathways have known presence-absence polymorphisms segregating in this population and should have *cis*-eQTL but none were detected by our analysis (Siewers, Viaud et al. 2005, Pinedo, Wang et al. 2008, Zhang, Corwin et al. 2018). Critically, the transcripts within each of these pathways are highly correlated across the isolates, suggesting that their expression variation is controlled by pathway-specific variation (Zhang, Corwin et al. 2018). Thus, these loci may have false-negative issues that prevented the detection of real *cis*-eQTL.

To test if these pathways have undetected *cis*-eQTL we used all of the SNPs for each biosynthetic cluster to investigate haplotype diversity across the *B. cinerea* isolates. We first investigated the botcinic acid cluster which identified a number of distinct haplotypes with a few individual outlier isolates (e.g. B05.10, Fd1) (Figure 3a). We then utilized the haplotypes to test for specific effects on transcript expression for the biosynthetic pathway. This identified a single clade of isolates with a distinctly lower level of expression than the other clusters (Figure 3b). Investigating the short-reads and SNP calls showed that these 12 isolates share a 53.5 kb deletion that removes the entire biosynthetic cluster, from Bcboa1 to Bcboa17 (Figure 3c). After removing the major deletion, we found no remaining significant effect of cluster membership in the remaining 3 major clusters on expression profile (F(1,74)=0.36, p=0.55). However, within each of these clusters there are independent isolates with very low pathway expression, suggesting loss-of-expression polymorphisms (Noble Rot, 01.04.03, Apple 517, 02.04.09) (Figure 3b). While these isolates each contain smaller deletions that are independent of each other, it is not clear what is functionally leading to the loss of botcinic acid biosynthetic pathway expression (Figure 3c). This suggests that for this clustered pathway, there are undetected *cis*-effect polymorphisms, a large common deletion and rarer additional events.



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