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Genomic signatures of disease resistance in endangered staghorn corals

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Materials and Methods

Tank-based disease resistance assays

Tank-based transmission experiments were conducted in Florida (July 2021) and Panama (November 2021) using 50 putative genotypes from each location. At each location, ten replicate fragments from each putative genotype were spread across one of ten 18-liter recirculating tanks held at ambient seawater temperatures at each location's flow-thru seawater system. Each fragment was experimentally lesioned with a waterpik to facilitate transmission (*17*). Five tanks were exposed to 50ml of disease slurry produced from 10 WBD infected coral fragments and five tanks were exposed to 50ml of healthy slurry from 10 healthy fragments. Slurries were produced by waterpiking disease or healthy coral tissue off the sampled corals in filtered seawater (FSW) and normalizing the slurry doses to a standard ocular density of 0.6 at 600nm. Exposed coral tanks were censused for disease twice daily at 6am and 6pm for up to 7 days and disease coral fragments were pulled from tanks at the first signs of disease to prevent amplifying pathogen spread within each tank.

The Florida transmission experiment was conducted over a period of 7 days at the Florida Keys Marine Laboratory between June 19 – 27, 2021 using replicate fragments from 50 putative coral genotypes sourced from the Coral Restoration Foundation (CRF) nursery located off Marathon, FL. The Panama transmission experiment was conducted at the Smithsonian Tropical Research Institute Station (STRI) in Bocas del Toro, Panama between November 6 – 12, 2021 using 50 putative coral genotypes sampled from 5 reefs located in Coral Cay; ten putative genotypes were sampled from each reef with each genotype sampled at least 5 meters apart to avoid collecting clones. The Panama transmission experiment was halted at day 6 due to high transmission rates.

To determine genotypic disease resistance, we used a Cox Proportional Hazards model using the time to infection as the response variable. Time to infection was modelled using a fixed effect of exposure with random effects of experiment location, and both genotype and tank nested within experimental location. Normalized disease resistance was calculated as one minus the mean predicted probability of infection of a given genotype six days post-exposure controlling for both experimental location and tank. The Cox proportional hazards model was fit using the R package MGCV (*50, 51*).

Genome assembly and annotation

A high-quality genome assembly was produced using high molecular weight DNA extracted from adult tissues of the CRF K2 genotype using SQK-LSK112 kit, three library preps run separately on three MinION flow cells (FLO-MIN112). Two libraries were not size selected while the third included 20+kb PippenPrep size-selection. High-quality base-calling was done

using Guppy v6.1.7 (Oxford Nanopore Technologies) and the output formed into an initial genome assembly using FLYE (*52*) with the nano-hq parameter setting to fit with the chemistry and base-calling method of the sequencing. After initial assembly of the raw nanopore reads, duplicated sequences were removed using purge_dups (*53, 54*). We polished the genome using two rounds of long read polishing with RACON (*55*) followed by a round of polishing with MEDAKA v1.7.2 (Oxford Nanopore Technologies) and then two rounds of polishing using 966 MB of high quality trimmed and contaminant filtered short-read paired 250 bp and paired 150 bp Illumina sequences from the K2 genotype using PILON (*56*). We corrected misassembly errors with short reads using MEC (*57*) followed by removal of the mitochondrial genome and other potential genomic contaminants using BLOBTOOLS (*58*). This was followed by misassembly correction using the long read data (*59*), scaffolding (*59*), gap closing (*60*), and a final round of long read polishing with RACON and short read polishing with PILON (*55*, *56*).

We used mRNA-seq data from 48 samples exposed to disease and healthy slurries from the Florida tank experiment as well as published RNA sequencing data from 38 additional *A. cervicornis* to assemble the transcriptome and annotate genes within the genome (PRJNA222758; *29*, PRJNA423227; *61*). RNA sequencing data were first quality filtered and decontaminated using fastp (*62*) and fastq_screen (*63*), and then assembled into a transcriptome using a genome-guided assembly in TRINITY (*64*). Genome annotation was performed using MAKER (*65, 66*). Briefly, this involved first identifying and masking repetitive elements in the genome using REPEATMODELER (*67*) and REPEATMASKER (*68*). An initial round of annotation was performed using as evidence the previously assembled transcriptome (see above) and proteins identified in either all Acroporids in the UniProt database (*69*) or the closest reference proteomes in UniRef from *Stylophora pistillata* (*70*), *Pocillopora damicornis* (*71*), *Actinia tenebrosa* (*72*) and *Nematostella vectensis* (*73*). This initial round of annotation was used to train the *ab initio* gene identification models of Augustus (*74*), Snap (*75*), and Genemark-ES (*76*). After the initial round of annotation based solely on protein and RNA evidence, we performed four subsequent rounds of annotation with the results of the previous round being used to train the *ab initio* gene predictors run in the subsequent round of annotation. Finally, after structural annotation of the genome we functionally annotated the identified genes using EnTAP (*77*) and InterProScan (*78*). Annotations for all candidate disease resistant genes (see below and main text) were manually curated with the InterProScan databases to ensure accuracy of the annotations and composition of protein domains (table S4).

Whole-genome sequencing and variant calling

Whole genome sequencing was produced for 96 putative *A. cervicornis* genotypes (48 from Florida and 48 from Panama) using Illumina DNA Prep kit on two 150bp paired-end NovaSeq S4 runs. Reads were quality controlled and decontaminated with fastp (*62*) and fastq_screen (*63*) which included 13 Symbiodiniaceae reference genomes (table S5). To determine if symbiont community composition varied between the two *A. cervicornis* populations or with normalized disease resistance, reads which mapped uniquely to one of the Symbiodiniaceae reference genomes and were analyzed at the genus level using a PERMANOVA with 1,000 permutations and visualized with an NMDS (*79*). We found no significant interactive effect of disease resistance and location on symbiont composition ($F_{(1, 72)} = 0.02$, $p = 0.78$) and no effect of disease resistance alone on algal symbiont composition ($F_{(1, 72)} = 0.04$, $p = 0.65$). There were significant differences in symbiont composition between Florida and Panama ($r^2 = 0.07$, $F_{(1, 72)} = 5.65$, $p = 0.012$, fig S3, table S5).

Genotypes and SNPs were called using ANGSD (*80*). To be identified as a SNP a locus required a minimum combined sequencing depth of 50x, a maximum combined sequencing depth no more than four standard deviations above the mean combined sequencing depth, and to be sequenced in at least 50% of individuals. Furthermore, loci required a minimum base and mapping quality of 30 and a maximum SNP p-value of 1×10^{-6}. A total of 1,795,328 bi-allelic SNPs were identified across the *A. cervicornis* genome. These SNPs were then filtered based on a minor allele frequency > 5%, and presence in at least 90% of individual samples with a posterior probability of genotype assignment > 99%. Individuals were removed from the sample if fewer than 30% of the loci were confidently genotyped (>99%). After filtering, there were a total of 1,193,166 loci. For analyses requiring unlinked loci (e.g. F_{ST}, PCA, and Structure analyses), loci were thinned to a set of 54,871 putatively unlinked loci with $r^2_{LD} < 0.5$. Clones within the samples were identified and removed based on having a multi-locus similarity > 97% (*81*; fig. S2). We found nine clone sets in both Florida and Panama with most sets being composed of two or three ramets with one clone group from Panama comprising eight total ramets. After retaining only the individual with the least missing data from each clone group, we were left with a sample of 76 unique genotypes (40 Florida, 36 Panama).

Population genetic analyses

Using the set of 54,871 unlinked loci, we calculated the average F_{ST} between Florida and Panama populations of *A. cervicornis* with significance assessed based on 1,000 permutations using HIERFSTAT (*82*, *83*). To visualize population structure and determine degree of admixture between populations we performed a principal component analysis using the unlinked loci and a STRUCTURE-like analysis in PCAngsd (*84*). Determination of the best number of clusters was based on minimization of cross-entropy using 10 replicate runs assuming the true number of clusters is between 1 and 10 (fig. S4).

Hybridization analysis

To determine if any historic introgression with the congener *A. palmata* is related to disease resistance, whole-genome sequencing data from *A. palmata* and the hybrid form *A. prolifera* were downloaded from NCBI BioProject PRJNA473816 (*85*). These sequences were pre-processed as above and mapped to the *A. cervicornis* genome. The filtered 54,871 unlinked SNP loci were called in the 28 *A. palmata* and 24 *A. prolifera* samples using ANGSD and further filtered to 53,740 unlinked SNP loci due to several not being well represented in the sequencing of *A. palmata* and *A. prolifera*. A F_{ST} of 0.15 was calculated between *A. palmata* and *A. cervicornis* as above. Further, we simulated 50 first- and second-generation hybrids and backcrosses between observed populations of *A. cervicornis* and *A. palmata* (*83*). We visualized and compared the observed versus the simulated hybrids using PCA to identify putative recent generation hybrids (Fig S6). There was no evidence that any *A. cervicornis* genotypes were recent backcrosses and disease resistance did not correlate with PC 1 ($r_\tau = 0.058$, $p = 0.46$), which separated both species indicating that disease resistance is not correlated to introgression history.

Genome-wide association tests

SNPs associated with disease resistance were identified using latent factor mixed model analysis accounting for population structure between the Florida and Panama samples implemented in LEA (*86*). Missing genotypes were imputed based on the modal genotype of the population to

which the sample belongs. P-values of loci were adjusted using the Benjamini-Hochberg (*87*) correction to control for false discovery.

After identification of candidate loci associated with disease resistance, we used clumping and thresholding (*88*) to identify potential effects of unlinked groups of loci and calculate a polygenic score for each individual. This process involves first clumping all loci with an $r^2_{LD} > 0.5$ within 250 kb with the locus with the minimum p-value. This was then repeated until all loci were clumped with an index SNP representative of the clump. The polygenic score of each individual was calculated using subsets of these clumps based on various thresholds of the index locus p-value. Finally, beta regressions were performed comparing the observed disease resistance (y) to the polygenic score (x) with the optimal threshold chosen based on maximization of r^2 (*88*; fig. S8). As disease resistance is an estimate, we incorporated the uncertainty in the measurement using inverse-variance weighting in the beta regressions (*89*). Regression q-q plots were visually inspected to ensure the normality of weighted residuals (*90, 91,* fig S9). The r^2 of each model was adjusted to account for overfitting using the optimism adjusted bootstrap technique with 100 bootstraps to mimic a train/test data split while allowing all samples to be used for PGS model inference (*92*).

Gene Expression Analysis

To determine if any of the five candidate disease resistance genes with functional, protein-coding changes, *PTPRD*, *AP3D1*, *SECG*, and *LRP2*, differed in their gene expression in response to exposure to White Band Disease, we analyzed mRNA-seq data from six genotypes from the Florida transmission experiment sequenced at three- and seven-days post exposure to the healthy and disease treatments. After RNA quality control (see genome assembly above), RNA expression was measured using HTSEQ mapping (*93*). Samples had an average of 20 million reads ± 1.3 million SE. Genes were then filtered to only analyze those found in 95% of samples, and not missing in more than 50% of a single treatment combination. Genes were further filtered to only analyze those which were expressed at a rate of at least 0.5 log2 cpm, and variance between 10 and 10,000 across all samples. Finally, any genes with a mean expression less than 5 were removed from the analysis. After filtering, genes were normalized using the trimmed mean of M-values method using EDGER (*94, 95*). We then analyzed differential gene expression using linear mixed effects models with the log2 cpm normalized reads per gene explained by the sampled timepoint, disease exposure, and disease resistance with genotype as a random effect. Model significance was assessed using the Kenward-Roger estimate of denominator degrees of freedom (*96*). We found no significant effects of time, disease exposure, or disease resistance on expression of *AP3D1*, *CFA61*, *LRP2*, or *PTPRD* (table S6, fig S10). *SECG* was not analyzed as it was filtered out from the genes to analyze for being expressed only at low levels (less than 0.5 log2 cpm) across all samples.

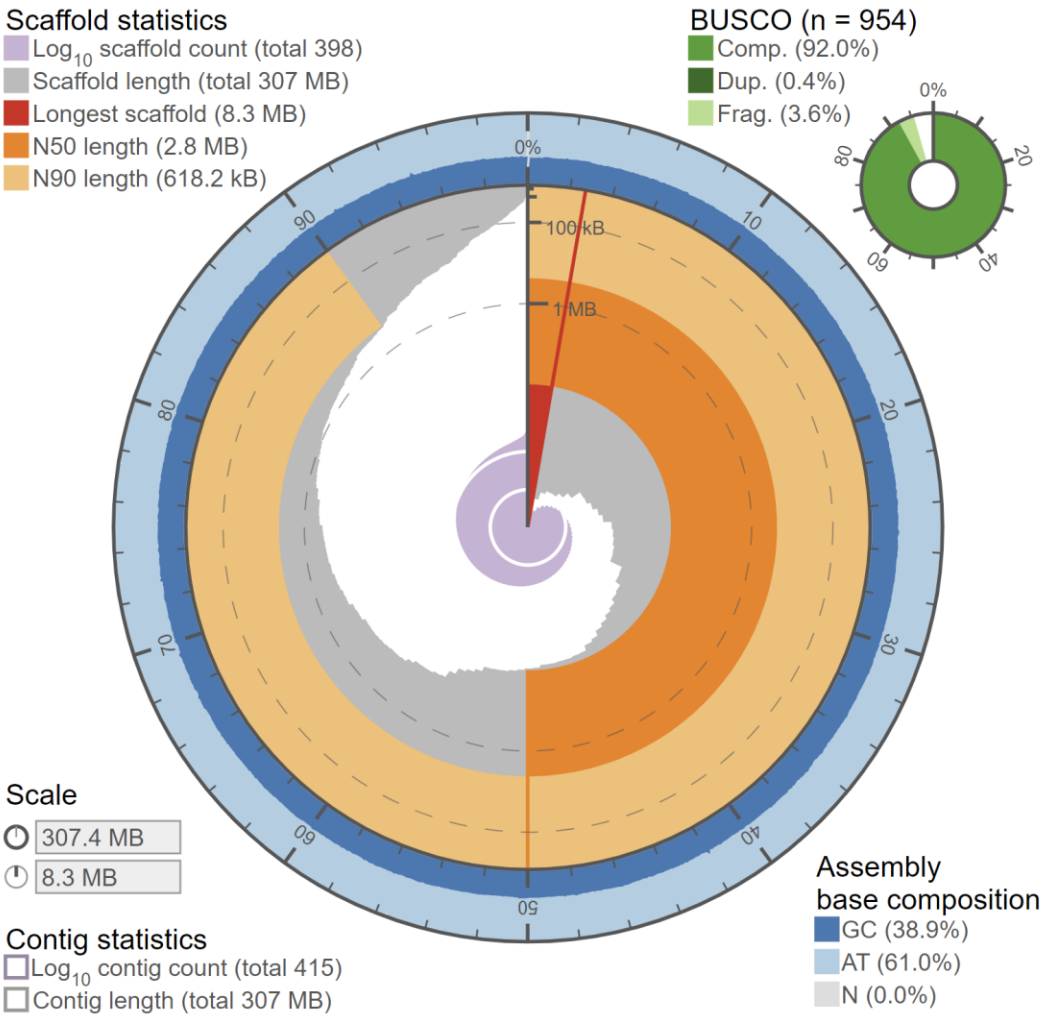

Figure S1: K2 genome assembly snail plot. For interactive version see: https://jdselwyn.github.io/assembly-stats/

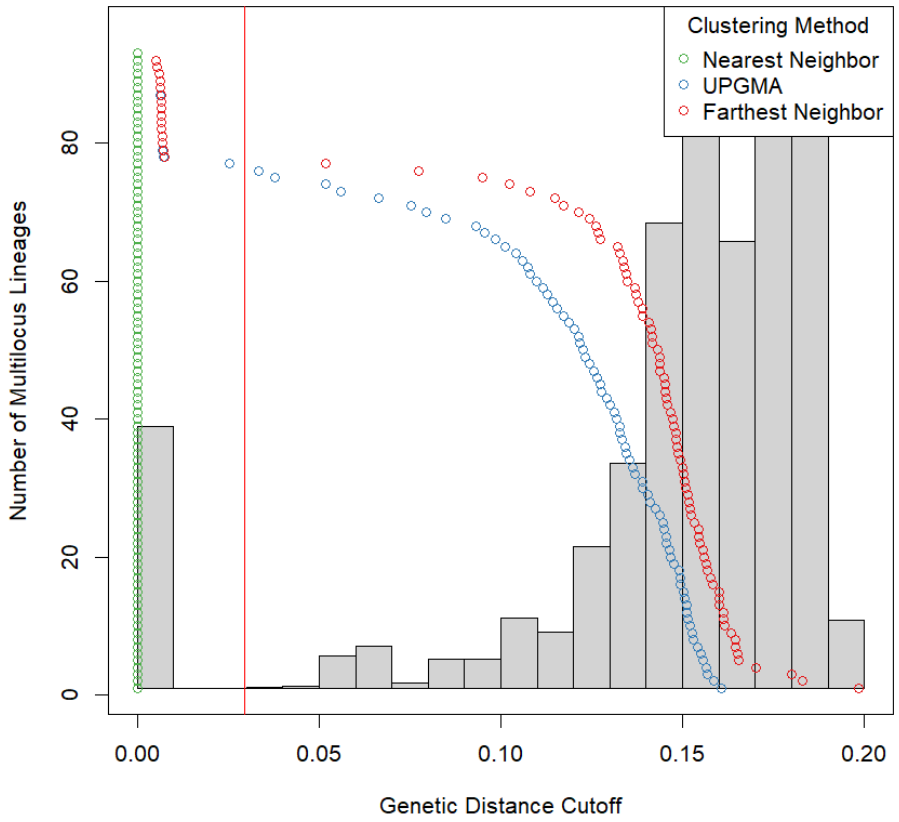

Figure S2: Figure showing pairwise genetic distance between coral ramets showing a cutoff of 2.97% similarity to use for removal of clones.

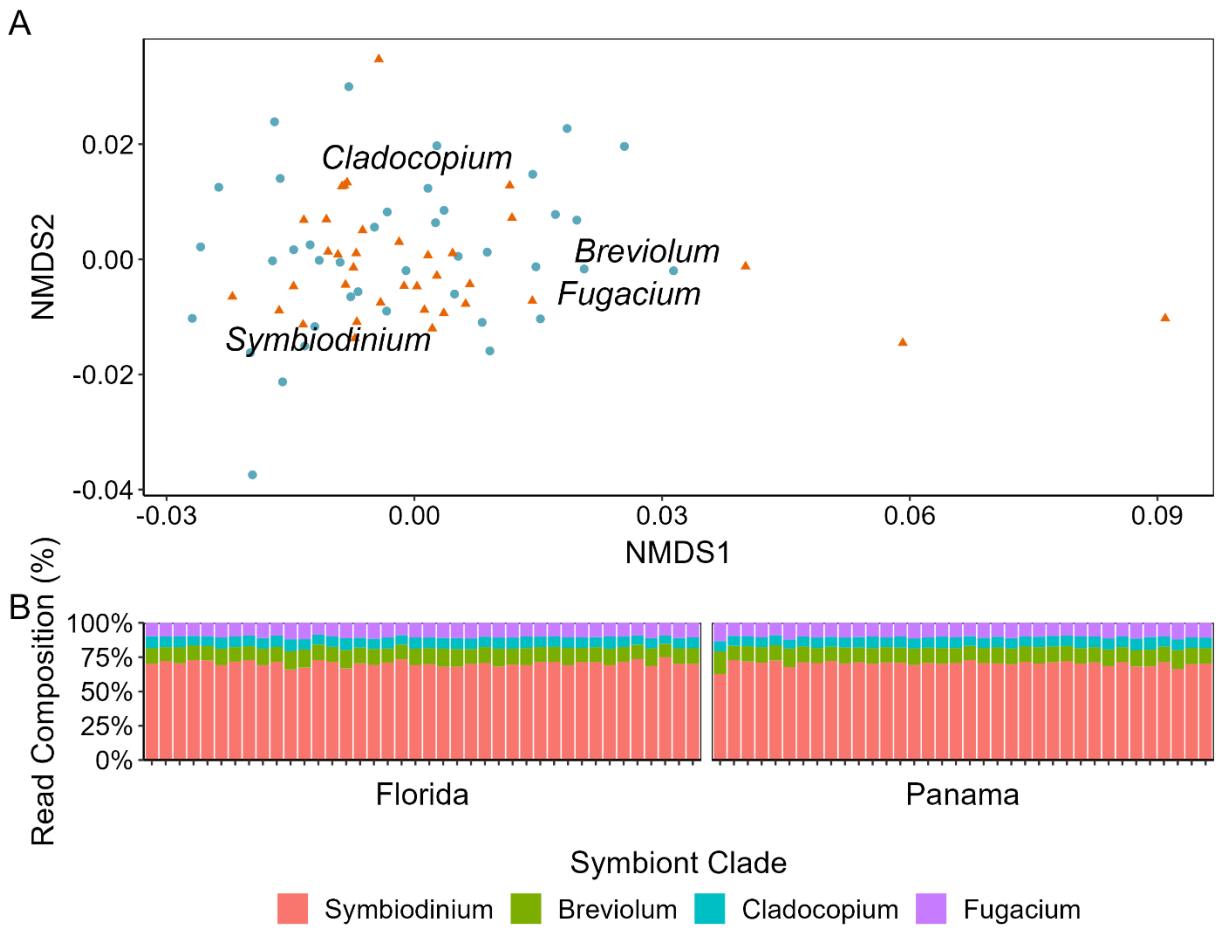

Figure S3: Visualization of the composition of algal symbiont reads detected in samples and disease resistance. A PERMANOVA with 1,000 permutations found no significant interactive effect of disease resistance and location on symbiont composition ($r^2 = 0.003$, $F_{(1, 72)} = 0.02$, $p = 0.78$) and no effect of disease resistance alone on algal symbiont composition ($r^2 = 0.008$, $F_{(1, 72)} = 0.04$, $p = 0.65$). There were significant differences in symbiont composition between Florida (blue) and Panama (orange, $r^2 = 0.07$, $F_{(1, 72)} = 5.65$, $p = 0.012$).

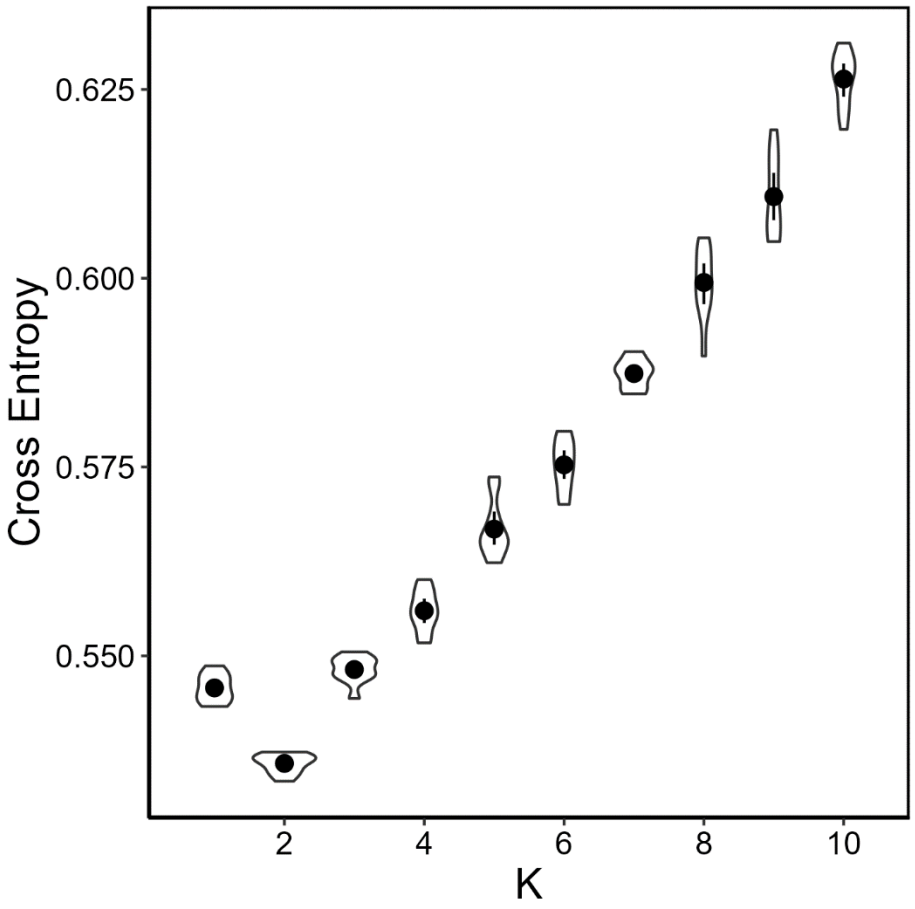

Figure S4: Cross-entropy from 10 independent STRUCTURE runs for each assumed true numbers of clusters (K) between 1 and 10.

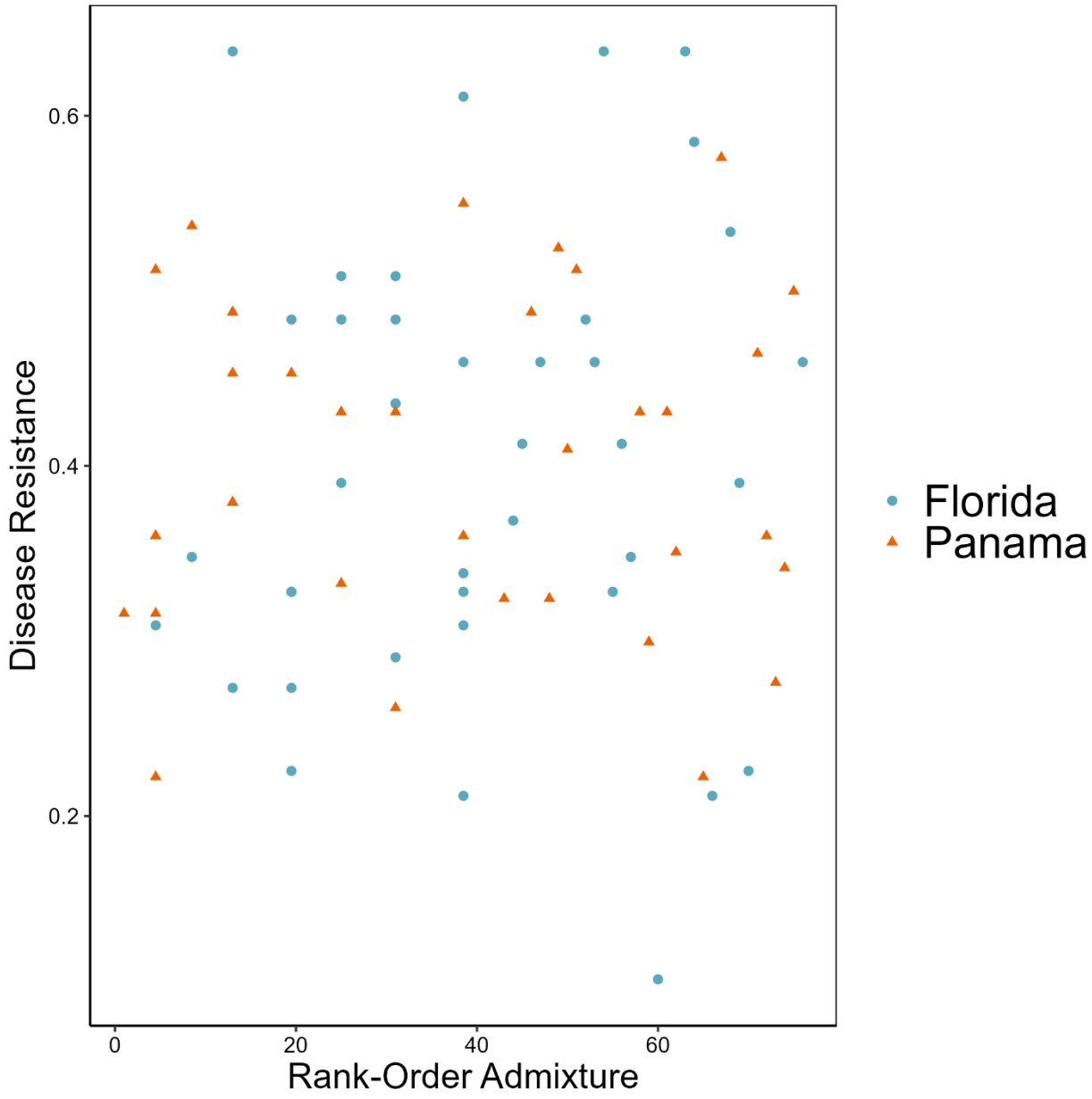

Figure S5: Plot of rank ordered degree of population-level admixture found in *A. cervicornis* fragments from Panama and Florida showing no correlation to disease resistance ($r_\tau = 0.05$, $p = 0.53$).

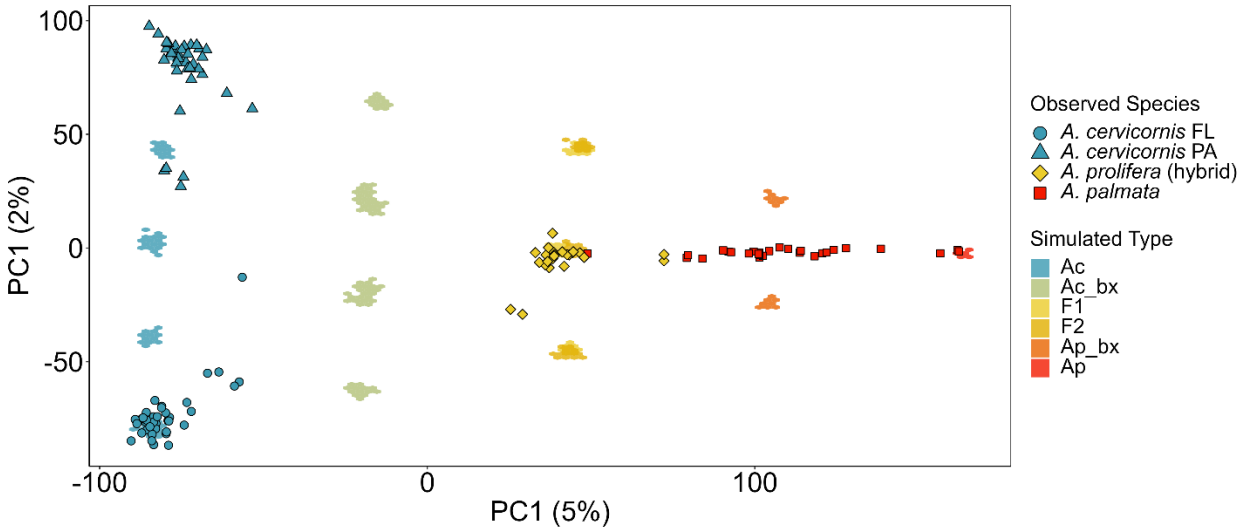

Figure S6: Plot of observed (black outline) samples of *A. cervicornis* from Panama and Florida as well as *A. palmata* and hybrids, known as *A. prolifera*. Lighter areas represent simulated offspring of various crosses of the two observed *A. cervicornis* populations and *A. palmata* along with second generation hybrids and backcrosses with the parental populations.

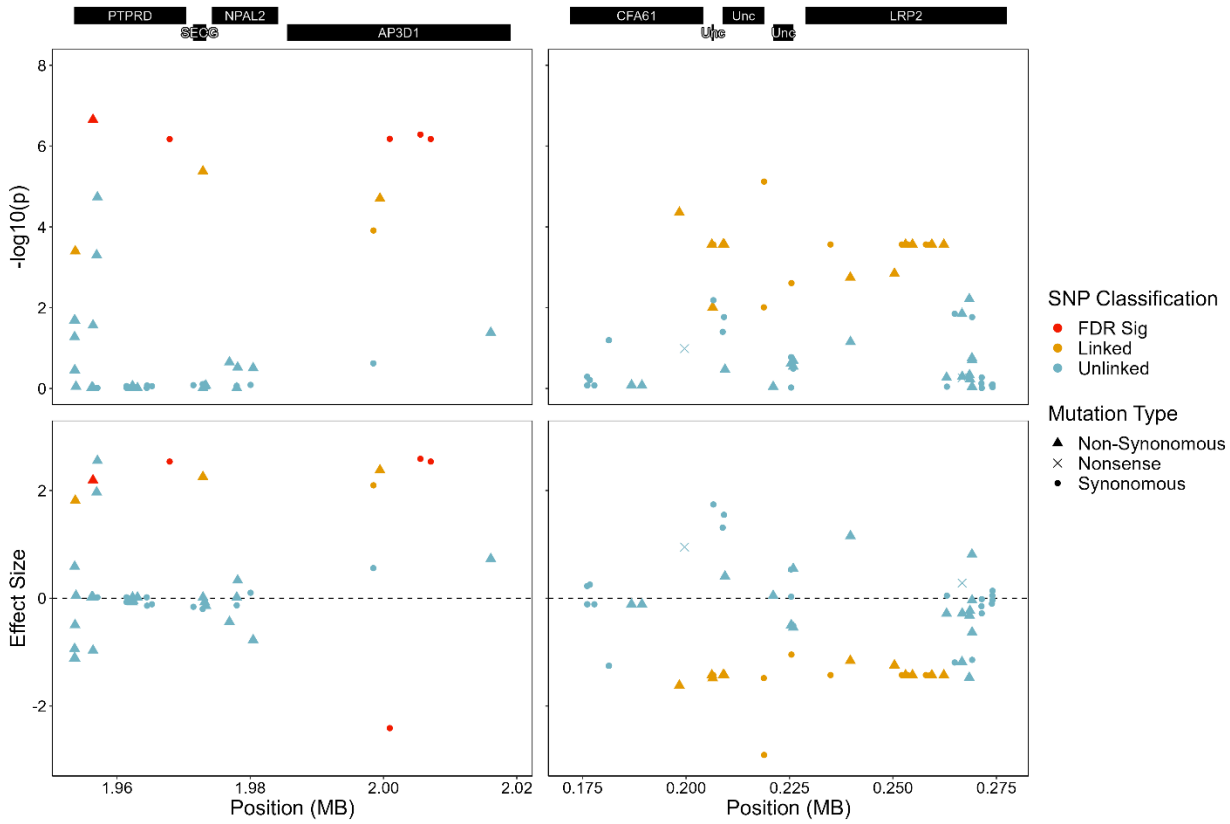

Figure S7: Genomic position of SNPs within genes in the region of significantly disease associated SNPs on chromosomes 8 and 142 indicating the mutation type (nonsynonymous, synonymous, or nonsense) and whether the locus is significant (FDR $p < 0.05$), linked to a significant locus, or not linked to a significant locus but in a gene.

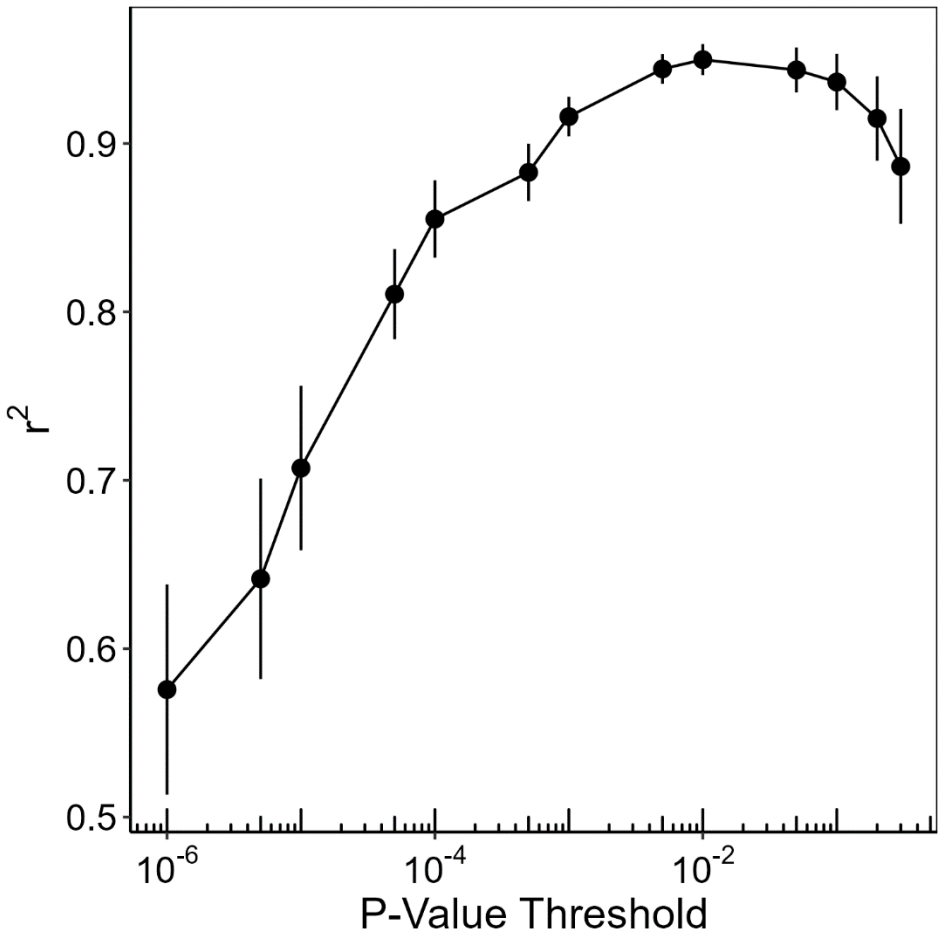

Figure S8: Plot of optimism adjusted r^2 (with standard deviation of bootstrap intervals shown) of the relationship between polygenic score and disease resistance versus the p-value threshold. The cutoff value chosen for clumping and thresholding was $p \leq 0.0001$ as the point of diminishing returns.

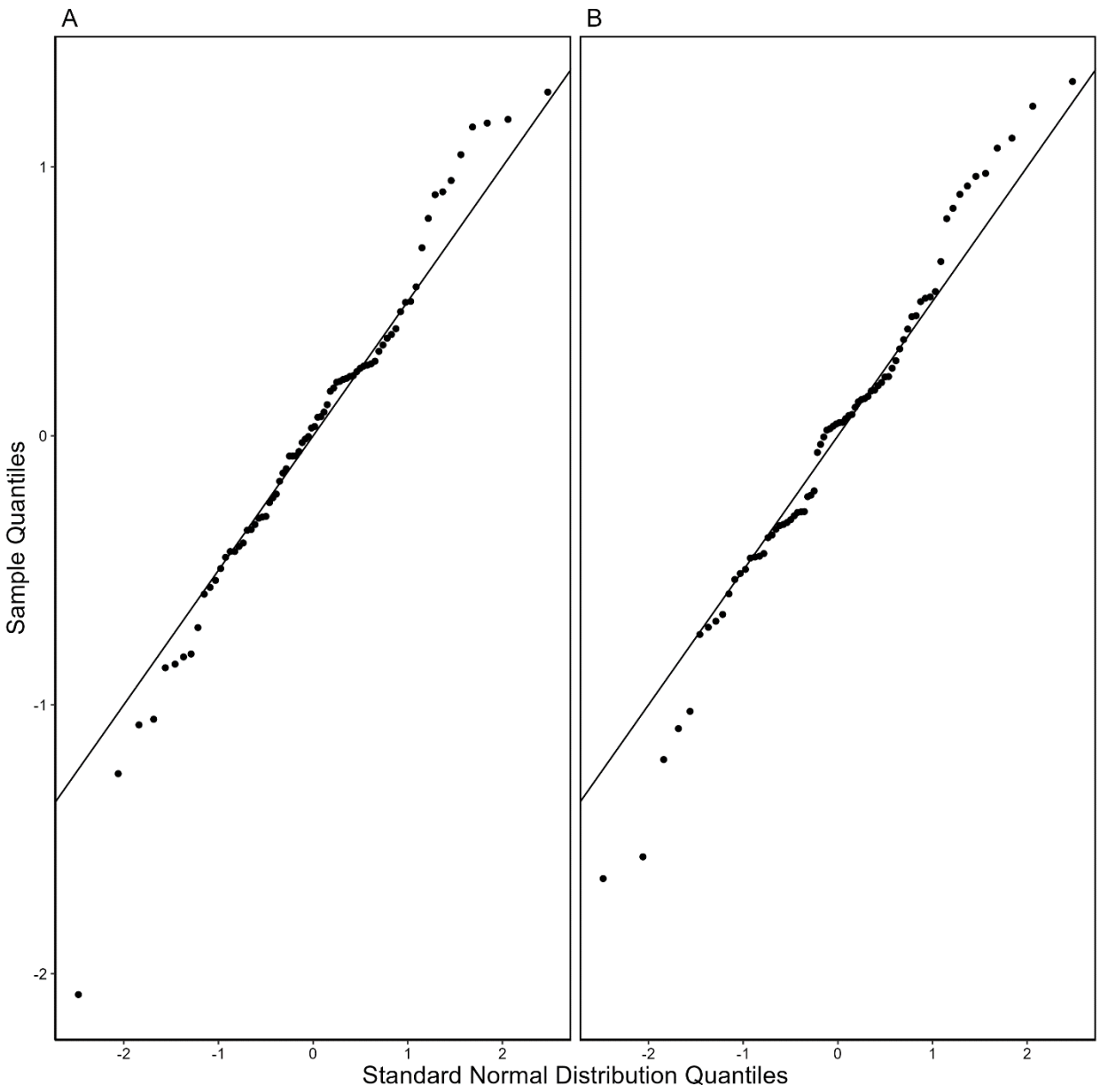

Figure S9: QQ-plot to assess the normality of standardized residuals of beta regressions of polygenic score calculated with 10 SNPs (A) and 63 SNPs (B) explaining disease resistance.

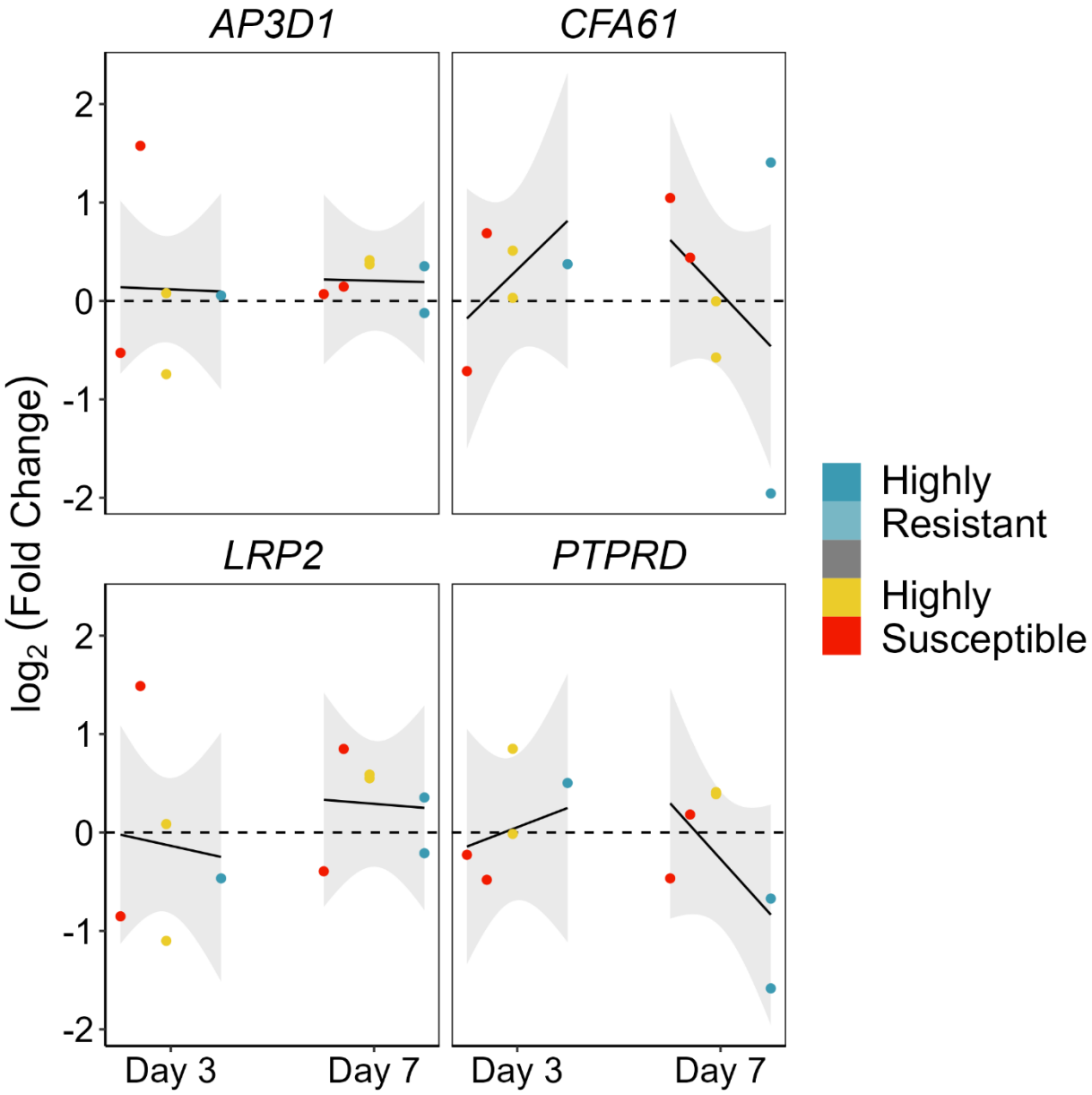

Figure S10: Gene expression plot showing mean and 95% confidence intervals of $\log_2$ (Fold Change) differences between disease exposed samples (positive) and healthy exposed samples (negative) for four genes with SNPs significantly associated with disease resistance (*AP3D1*, *CFA61*, *LRP2*, and *PTPRD*). Points show disease resistance and expression of each sampled genotype with color indicating the observed disease resistance. Linear mixed effects models for each gene found no significant effects of exposure, time (x-axis), disease resistance (sub x-axis), or any interactions (all $p > 0.05$, table S6).

Table S1: Table of SNP loci significantly associated with disease resistance and linked loci. Including gene annotations, mutation type, and linkage group. Available as downloadable CSV files due to its large size.

Table S2: Table of SNP loci used to calculate polygenic score in both SNP sets. Available as downloadable CSV files due to its large size.

Table S3: National Center for Biotechnology Information accession numbers and citations for *Symbiodiniaceae* reference genomes which reads were mapped against to identify *Symbiodiniaceae* composition within each sample. Species names have been adjusted *sensu* LaJeunesse et al. 2018 (*97*).

Species	Clade	Accession #	Citation
Symbiodinium microadriaticum	A	GCA_001939145	Aranda et al 2016 (*98*)
Symbiodinium sp. clade A Y106	A	GCA_003297005	Shoguchi et al. 2018 (*99*)
Cladocopium sp. clade C Y103	C	GCA_003297045	Shoguchi et al. 2018 (*99*)
Fugacium kawagutii	F	GCA_009767595	Lin et al. 2015 (*100*)
Symbiodinium microadriaticum	A	GCA_018327485	Yoshioka et al. 2021 (*101*)
Symbiodinium natans	A	GCA_905221605	González-Pech et al. 2021 (*102*)
Symbiodinium sp. CCMP2592	A	GCA_905221615	González-Pech et al. 2021 (*102*)
Symbiodinium sp. KB8	A	GCA_905221625	González-Pech et al. 2021 (*102*)
Symbiodinium sp. CCMP2456	A	GCA_905221635	González-Pech et al. 2021 (*102*)
Symbiodinium pilosum	A	GCA_905231905	González-Pech et al. 2021 (*102*)
Symbiodinium necroappetens	A	GCA_905231915	González-Pech et al. 2021 (*102*)
Symbiodinium microadriaticum	A	GCA_905231925	González-Pech et al. 2021 (*102*)
Breviolum minutum Mf 1.05b.01	B	GCA_000507305	Shoguchi et al 2013 (*103*)

Table S4: InterProScan results for candidate disease resistant genes available as downloadable CSV files due to its large size.

Table S5: PERMANOVA table testing the effect of location and disease resistance on algal symbiont community composition. The table indicates the degrees of freedom (df), sum of squares (SS), r^2, pseudo-F statistic (F) and p-values (p).

	df	SS	r^2	F	p
Location	1	0.321	0.071	5.65	0.012
Disease Resistance	1	0.037	0.008	0.65	0.478
Location * Disease Resistance	1	0.012	0.003	0.20	0.781
Residual	72	4.132	0.918		
Total	75	4.500			

Table S6: ANOVA tables evaluating the differential gene expression of the genes *AP3D1*, *CFA61*, *LRP2*, and *PTPRD* at different timepoints, disease exposures, disease resistances, and all their interactions.

Gene	Term	SS	F-statistic$_{(nDF, dDF)}$	p
AP3D1	Time	0.581	$F_{(1, 11.246)} = 3.663$	0.081
	Exposure	0.042	$F_{(1, 11.246)} = 0.266$	0.616
	Disease Resistance	0.016	$F_{(1, 4.229)} = 0.102$	0.765
	Time X Exposure	0.002	$F_{(1, 11.246)} = 0.011$	0.918
	Time X Disease Resistance	0.077	$F_{(1, 11.692)} = 0.486$	0.499
	Exposure X Disease Resistance	0.001	$F_{(1, 11.692)} = 0.005$	0.943
	Time X Exposure X Disease Resistance	0	$F_{(1, 11.692)} = 0.000$	0.985
CFA61	Time	0.547	$F_{(1, 11.225)} = 1.527$	0.242
	Exposure	0.065	$F_{(1, 11.225)} = 0.180$	0.679
	Disease Resistance	0.063	$F_{(1, 4.229)} = 0.176$	0.695
	Time X Exposure	0.453	$F_{(1, 11.225)} = 1.263$	0.285
	Time X Disease Resistance	0.204	$F_{(1, 11.641)} = 0.571$	0.465
	Exposure X Disease Resistance	0.001	$F_{(1, 11.641)} = 0.004$	0.951
	Time X Exposure X Disease Resistance	0.78	$F_{(1, 11.641)} = 2.177$	0.167
LRP2	Time	0.55	$F_{(1, 11.200)} = 2.180$	0.167
	Exposure	0.042	$F_{(1, 11.200)} = 0.168$	0.689
	Disease Resistance	0.384	$F_{(1, 4.225)} = 1.522$	0.282
	Time X Exposure	0.032	$F_{(1, 11.200)} = 0.129$	0.727
	Time X Disease Resistance	0.149	$F_{(1, 11.580)} = 0.591$	0.457
	Exposure X Disease Resistance	0.017	$F_{(1, 11.580)} = 0.068$	0.798
	Time X Exposure X Disease Resistance	0.004	$F_{(1, 11.580)} = 0.015$	0.905
PTPRD	Time	0.908	$F_{(1, 11.192)} = 3.108$	0.105
	Exposure	0.028	$F_{(1, 11.192)} = 0.096$	0.763
	Disease Resistance	0.146	$F_{(1, 4.223)} = 0.498$	0.517
	Time X Exposure	0.171	$F_{(1, 11.192)} = 0.584$	0.461
	Time X Disease Resistance	0.045	$F_{(1, 11.558)} = 0.153$	0.702
	Exposure X Disease Resistance	0.099	$F_{(1, 11.558)} = 0.340$	0.571
	Time X Exposure X Disease Resistance	0.421	$F_{(1, 11.558)} = 1.440$	0.254

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