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**Article title:** Rapid Evolutionary Response to a Virulent, Introduced Parasite in Darwin’s Finches

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Data and materials availability: All sequencing data are uploaded to NCBI’s Sequencing Read Archive and will be made publicly available upon acceptance. All code used in these analyses can be found on GitHub and will be archived permanently upon acceptance (<https://github.com/dannyjackson/DarwinFinches>).

**Abstract:**

Selection from parasites shapes biodiversity, but insights into the early stages of host evolution in response to novel parasites are rare. Darwin’s finches face severe impacts from the avian vampire fly, which was introduced to the Galápagos in 1997. Larvae of the fly suck the blood of nestling birds and drive steep reductions in fledging success. We sequenced genomes of three species of Darwin’s finches and tested for evidence of selection over 22 years of exposure to a novel ectoparasite. We found strong evidence of selection in the vegetarian finch, the most tolerant to the avian vampire fly, on genes involved in blood vessel development and immune function. We also found evidence of selection on immune-related genes in the medium ground finch, and sparse evidence of selection in the small tree finch. Finally, we document evidence of parallel selection on three genes across all three species involved in angiogenesis and immune function.

Parasites exert some of the strongest selective forces on host taxa, yet the evolutionary dynamics of animal hosts in response to novel parasitic challenges are poorly understood. While experimental studies have provided valuable insights, natural instances of novel host-parasite relationships are rare (Jackson et al. 2025). Human-mediated introductions of parasites provide a unique opportunity to document evolution of a wild host population during the initial stage of host-parasite coevolution, to characterize the timeline over which selection on hosts is detectible, and to determine the extent to which adaptation is predictable across hosts in response to novel parasites (*1*). Such insights are essential for understanding the increasing threat posed by novel parasites and emerging disease to biodiversity worldwide.

Darwin’s finches are the canonical example of evolution by natural selection. They are best associated with the evolution of morphological traits over short time scales in response to fluctuating climate conditions and competition for food (*2*–*4*). This clade comprises 18 species in the tanager family (Thraupidae), 17 of which are endemic to the Galápagos Islands and one to Cocos Island, that have diversified over the past 1-2 million years (*5*). The recent arrival of a virulent, introduced parasite has reshaped the selective landscape for Darwin’s finches. In 1997, larvae of the avian vampire fly (*Philornis downsi*) were first observed in the nests of breeding birds in the Galápagos (*6*). The larvae of the vampire fly live in the nests of birds and feed on the blood and tissue of nestlings, causing anemia, reduced body condition, life-long craniofacial damage, and often death (*7*). This parasite has become pervasive in the Galápagos. On Santa Cruz Island, nearly 100% of finch nests are parasitized and nestling mortality from parasitism ranges from ~ 40 – 100% (*7*, *8*). The vampire fly has contributed to the decline of several endemic passerine species, including two species of Darwin’s finch, the Mangrove finch (*Camarhynchus heliobates*) and the medium tree finch (*C. pauper*) (*4*). The consequences of this striking new selective pressure on the evolutionary trajectory of these iconic species are unknown. Insights from this system could inform our understanding of rapid evolution in response to human-mediated environmental changes.

We conducted whole genome sequencing on three species of Darwin’s finch, the medium ground finch (*Geospiza fortis),* the small tree finch (*Camarhynchus parvulus*) and the vegetarian finch *(Platyspiza crassirostris*). We sequenced 24 samples collected in 2019, 22 years after the first observation of vampire fly larvae in the Galápagos in 1997 (*7*) and compared them to previously sequenced pre-invasion samples collected in the 1980s and 1990s (table 1) (*10*), generating a genomic time-series spanning the period before and after the introduction of the parasite. Birds from both sampling time points were collected on Santa Cruz Island and were sequenced to the same depth of coverage (~10x) using 2 x 125 base-pair paired-end reads. All were aligned to the STF\_HiC small tree finch genome (1.28 GB; Genbank accession number: GCF\_901933205.1) (*6*). Analyses were conducted using a genotype likelihood framework. A total of 8,572,849 putatively polymorphic sites passed a SNP p-value threshold of 1e-6 in ANGSD (*12*). Disentangling the signals of selection from those of drift over such a short time frame (~3.5-7 generations) is challenging, so we used a conservative approach that identified outlier genomic regions with evidence of both divergence over time and shifts in the site frequency spectrum associated with selective sweeps. We calculated FST and ∆Tajima’s D in 50kb windows with a 12.5kb step in ANGSD. Both statistics were scaled and centered, and we took the inverse of ∆Tajima’s D to align the direction of significance between the two metrics. We classified outliers as the top 0.1% windows of the sum of the scaled and centered FST and the inverse of ∆Tajima’s D. Genes that overlapped with any portion of the outlier windows were identified as putative targets of selection. We used a less conservative cutoff of 1% to test for parallel selection on the same genes across all three species. We tested for overrepresented Gene Ontology (GO) terms associated with genes within the outlier windows from our additive model of *Z-*FST and the inverse of *Z-*∆Tajima’s D for each species. Finally, we examined the function of each gene associated with a significant GO term, as well as the potential effects of single nucleotide polymorphisms (SNPs) within those genes.

**Low genome-wide divergence over 20 years of selection**

All three species showed low levels of divergence between the two time points (Genome-wide FST = 0.029-0.038, maximum windowed FST = 0.299-0.369, Fig. S3, table S1). Historic population size inferences in MSMC could change over time in the presence of novel patterns of introgression or gene flow (*13*); however, we did not observe differences between models of pre- and post-invasion samples in any species (Fig. S2).

**Signals of selection in response to parasitism emerged from two species**

Genomic changes since the introduction of the fly were associated with significantly overrepresented GO terms in two of three focal taxa: the medium ground finch and the vegetarian finch. The overrepresented categories for the medium ground finch were associated with regulation of various metabolic processes. In the vegetarian finch, significant GO terms were associated with blood vessel development or immune function, i.e., biological phenotypes that likely are under selection from the parasite (Table 2). This remarkable finding of genes involved in blood vessel development under selection in a host taxon by a blood sucking fly only ~20 years after its introduction demonstrates the extreme impacts of this novel parasite. It is also notable that we only observed this signal in the vegetarian finch, which exhibits the highest tolerance for parasitism by the avian vampire fly of all Darwin’s finches (6, 8). Four genes drove the angiogenesis signal in the vegetarian finch: *ANGPT1*, *ITGA2B, HPSE*, and *PODXL*. (*14*)(*15*, *16*)*HPSE* encodes the enzyme heparanase, which regulates clotting, inflamation, and the innate immune response, among other functions (*17*, *18*). *PODXL* encodes the protein Podocalyxin Like-1 which is found in hematopoetic progenetior cells and plays a role in the production of new blood cells (*19*).

The overrepresented categories for the medium ground finch were associated with regulation of various metabolic processes. Seven genes drove the signal for these overrepresented GO terms, and four of these genes have associations with blood physiology or immune functions. *CHST4* influences lymphocyte adhesion onto endothelial cells, *CELF1* affects heme oxygenase-1 (*20*), *TERF2IP* regulates of innate and adaptive immune function, inflammation (*21*), and *PRTFDC1* suppresses immune related pathways (*22*). The remaining three – *ADAT1*, *FARS2*, *MCM9* – are involved in gene expression and DNA-related processes (*23*–*25*).

While no GO terms were significant in the small tree finch, regions of the genome did show local peaks in our composite statistic (Fig. S3). This result suggests selection on some genes, although perhaps without a strong enough signal of selection across multiple genes involved in a single biological process. Our findings do not rule out ongoing selection on relevant physiological processes that could be better detected over a longer time period. These findings may help explain why the small tree finch appears particularly vulnerable to parasitism by the vampire fly. Experimental studies have shown that compared to other co-occurring hosts, the small tree finch suffers particularly high mortality due to the avian vampire fly (*26*, *27*). In fact, over the past two decades, the small tree finch has experienced higher parasite burdens in nests and suffers a higher loss of reproductive success due to parasitism than the smaller warbler finch (*Certhidea olivacea*) (*27*).

Candidate genes under selection were associated with blood physiology and immune functions in both the vegetarian finch and the medium ground finch, but the strength and nature of these signals differed between species. In the vegetarian finch, selection on genes related to blood physiology drove significance in several GO terms, suggested a concerted polygenic response in this phenotype. In contrast, the medium ground finch showed a broader pattern of selection across genes involved the innate and adaptive immunity, though no immune-related GO terms were significantly overrepresented. These early genomic responses may hint at divergent host strategies in response to the avian vampire fly. Resistance limits parasite burden, often through immune response, while tolerance mitigates the costs of parasitism without reducing parasite load. In the vegetarian finch, selection on genes related to blood physiology may reflect an emerging tolerance strategy by limiting resource availability to parasites. In contrast, selection on immune-related genes in the medium ground finch could support the potential for either resistance or immune-mediated tolerance. Upregulation of immune activity might confer resistance, whereas downregulation of an ineffective immune response could reduce energetic costs and favor tolerance. Notably, parasitized nestling medium ground finches do not mount an antibody-mediated response, although parasitized brooding females do (*28*). While we cannot yet determine whether these responses reflect an evolution of resistance, tolerance, or both, they clearly highlight different phenotypic targets of selection between the species.

**Angiogenesis and immune functions are under selection in the vegetarian finch**

Two of the four genes underlying the angiogenesis signal in the vegetarian finch, *ANGPT1* and *ITGA2B*, contain noncoding blocks of single nucleotide polymorphisms (SNPs) with high FST, which occur between exon 1 and 2 in *ANGPT1* and in the region immediately following *ITGA2B*. No SNPs were found in coding regions, nor were any SNPs in a CpG site, but the high FST region near *ITGA2B* is within 1kb and could affect a promoter region. These candidate genes suggest that the avian vampire fly is exerting strong pressure on blood physiology and wound healing in its hosts. The fact that these genes were identified in the vegetarian finch is notable, because this is the only species of Darwin’s finch that demonstrates tolerance to parasitism (*29*). Although heavily parasitized, nestling vegetarian finches experience relatively low (~20%) mortality due to parasitism. The vegetarian finch is the largest of Darwin’s finch species, and the corresponding larger size of its nestlings is thought to be one explanation for why nestlings can tolerate the fly. Nevertheless, the virulence of the avian vampire fly in different Galapagos hosts is imperfectly correlated with host size, suggesting that other biological differences may underlie host defense or susceptibility. Our results point to the rapid evolution of genes in the vegetarian finch since the introduction of the fly that could underlie adaptation of this host species to parasitism.

**Adaptive regulatory and protein-coding changes of blood-related genes in the vegetarian finch**

Two of the genes that drove the signal of selection on angiogenesis in the vegetarian finch, *HPSE* and *PODXL*, exhibited SNPs with relatively high FST in transcribed regions. Given the relevance of these functions to facilitating an evolutionary response to a blood-sucking parasitic fly, we further explored the putative functional changes associated with these temporally-divergent genotypes.

We found one SNP within the transcribed region of *HPSE* with a relatively high FST (0.327), specifically within the 3`UTR. RNA-binding proteins (RBPs) that bind to the 3`UTR regulate gene expression, and we used RBPmap (*19*) to predict RBP binding sites that may differ between the ancestral and derived allele in this region. We found one binding motif associated with both the derived and ancestral genotype (wgcaugm), and two associated only with the derived genotype (cgucca and rygcgcb) (table 3). In all three circumstances, the derived genotype matched the motif and the ancestral did not. The derived allele at this site increased from a frequency of 0.5 pre-invasion to 0.875 post-invasion, suggesting selection for an increased ability to regulate *HPSE* using miRNA.

We found five mutations within the coding sequence of *PODXL*, four of which were synonymous but one of which (P295A) was a missense mutation. We used SIFT to predict if this mutation resulted in a nonfunctional protein and found that it is expected to be tolerated (tolerance score = 0.35, median sequence conservation 4.32) (*13*), but it may have impacts on protein folding and structure. The frequency of this mutation decreased over time from 1.0 to 0.333, indicating selection against the derived protein.

**Intronic CpG mutations underlie parallel signals of selection on genes related to inflammation and angiogenesis**

We investigated the extent to which parallel evolution occurred in response to the fly by comparing candidate genes identified in the top 1% of windows scored by our composite statistic. We found significant overlap in genes under selection in all pairwise comparisons between species (Fig. 2A). We identified 32 genes in both the vegetarian and medium ground finch (OR = 3.32 [2.20 – 4.86], q < 0.001), 30 in both the vegetarian and small tree finch (OR = 2.18 [1.44- 3.21], q < 0.001), and 14 in both the medium ground finch and the small tree finch (OR = 1.83 [1.04 - 3.01], q = 0.030). GO term analysis of genes identified in two or more species found no significantly overrepresented terms. However, the three genes identified in all species, *BMPER*, *NUDT4*, and *TENM3*, have functions in biological processes relevant to a response to parasitism by the vampire fly. *BMPER* encodes the protein Bone Morphogenetic Protein-binding Endothelial Regulator, which facilitates endothelial cell sprouting, an essential step in angiogenesis (*32*). It also regulates dysregulated systemic inflammation at injury sites (*33*). *TENM3* encodes the protein Teneurin Transmembrane Protein 3 which influences the developing craniofacial mesenchyme and dermis (*34*, *35*). *NUDT4* encodes the protein Nudix Hydrolase 4 and has been identified as a key gene involved in sepsis (*36*), and is correlated with the abundance of various immune cells (*37*), and is also upregulated during erythropoiesis (*38*). We identified CpG sites with relatively high FST values within the intronic regions of each of the three genes in each of the three species (Fig. 2B, table S3). While all three species showed selection on these three genes, distinct alleles were under selection with little consistency in the directional change of allele frequencies (Fig. 2C). All CpG sites in *NUDT4* decreased in frequency following invasion of the vampire fly, while CpG sites in *BMPER* and *TENM3* decreased for the small tree finch, increased for the vegetarian finch, and both increased and decreased for the medium ground finch. In the small tree finch, we also identified a CpG site within the 5’-UTR of *NUDT4* that decreased from a frequency of 0.4 to 0 in the post-invasion samples. These results demonstrate evidence of selection for and against various regulatory sites, with species-specific trends. This sparse evidence of parallel in selective responses across taxa contrasts to the stronger findings from within taxa, such as the parallel allele frequency changes in immune genes in European rabbits (*Oryctolagus cuniculus*) in response to the myxoma virus (*1*).

We document evidence of rapid selection in response to a novel parasite in the vegetarian finch, the only taxa in the clade that does not experience high costs associated with parasitism by the vampire fly. Our results suggest that this host’s tolerance to parasitism may have increased over time through selection on standing variation in regulatory regions of angiogenesis and clotting genes. Through comparisons across all three taxa, we document evidence of parallel selection on three genes involved in blood clotting, craniofacial and dermis development, and immune function especially as it relates to sepsis. These findings suggest that fitness reductions are driven by blood loss, tissue damage, and a costly immune response that depletes the limited resources of developing nestlings. The major implications of our study are that novel parasites drive rapid evolution in hosts, that some similarities emerge across species in their responses to virulent parasites, but that species-specific genetic variation in a handful of loci may determine whether a species can evolve tolerance or not. Our evidence of early signals of a selective response demonstrates that studies into the early stages of ongoing selective events can illuminate mechanisms of adaptation or the lack thereof for species that face increasing threats from human-introduced parasites.

**Table 1:** Counts of individuals sequenced and population genetic statistics that compare pre- and post-invasion sequences.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Common name** | **Species** | **No.pre-invasion** | **No. post-invasion** | **FST** | **∆Tajima** |
| Vegetarian finch | *Platyspiza crassirostris* | 5 | 9 | 0.038 | 0.338 |
| M. ground finch | *Geospiza fortis* | 10 | 8 | 0.031 | -0.176 |
| S. tree finch | *Camarhynchus parvulus* | 12 | 7 | 0.029 | -0.173 |

**Table 2:** Significantly overrepresented GO terms and FDR corrected q-values from candidate gene lists of each species, and from the list of candidate genes identified in two or more species (pairwise overlap).

|  |  |  |  |
| --- | --- | --- | --- |
| **Species** | **PANTHER GO-Slim Biological Process** | **GO Term** | **q-value** |
| Vegetarian finch | regulation of cell adhesion mediated by integrin | GO:0033628 | 0.043 |
|  | angiogenesis | GO:0001525 | 0.014 |
|  | blood vessel morphogenesis | GO:0048514 | 0.011 |
|  | blood vessel development | GO:0001568 | 0.008 |
|  | vasculature development | GO:0001944 | 0.007 |
|  | tube morphogenesis | GO:0035239 | 0.005 |
|  | tube development | GO:0035295 | 0.006 |
| Medium ground finch | tRNA metabolic process | GO:0007519 | <0.001 |
|  | nucleic acid metabolic process | GO:0060538 | <0.001 |
|  | nucleobase-containing compound metabolic process | GO:0007517 | <0.001 |
|  | heterocycle metabolic process | GO:0060537 | <0.001 |
|  | cellular aromatic compound metabolic process | GO:0010720 | <0.001 |
| Small tree finch | None | None | NA |
| Pairwise overlap | None | None | NA |

**Table 3**

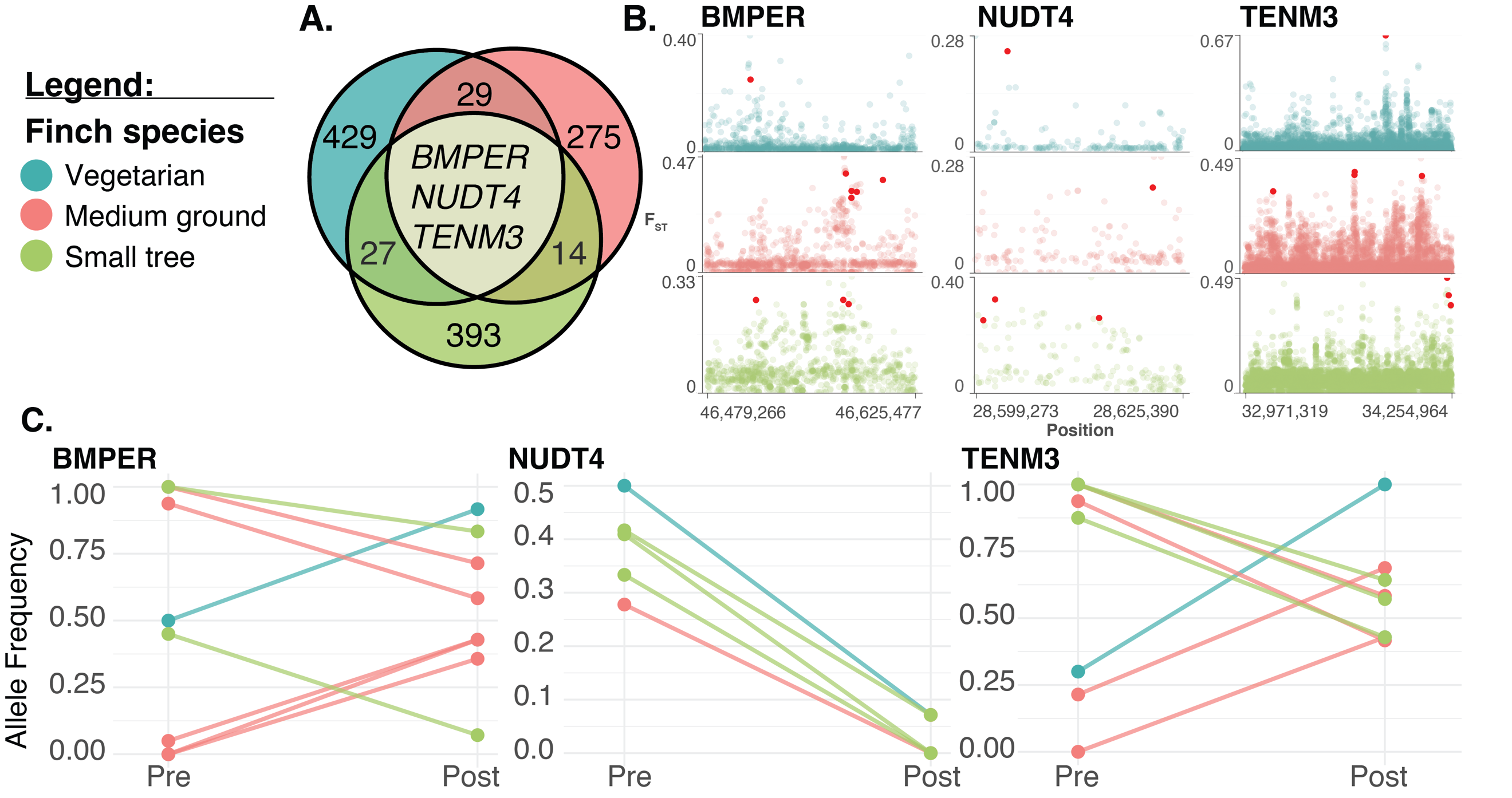
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Motif** | **Ancestral** | **Z-score** | **P-value** | **Derived** | **Z-score** | **P-value** |
| wgcaug**m** | ...g..**g** | 2.855 | 0.0022 | ...g..**c** | 3.329 | 0.0004 |
| cguc**c**a | ...g**g**. | NA | NA | ...g**c**. | 2.241 | 0.0125 |
| ryg**c**g**cb** | ...u.ga | NA | NA | ...u.**c**a | 1.784 | 0.0372 |

**Figure 1:** Manhattan plots of composite statistic for each species. The genes associated with a significant GO term identified for a particular species are mapped to the plot and presented in the color theme of the respective species. The three genes in black were identified as candidate genes in analyses of parallel evolution across all three species.

A diagram of a number of colorful lines

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**Figure 2: A**. Counts of candidate genes identified in the top 1% of windows of each species using the composite statistic. Only three genes were found in all three species, *BMPER*, *NUDT4*, and *TENM3*. **B**. Manhattan plots of FST values for every site within each gene, defined as the coordinates in the gff file. Bright red points represent SNPs with high FST and a polymorphism where one haplotype has a CpG site and the other does not. The three genes are from chromosome 2, 1A, and 4, respectively; genes are presented in alphabetical order. **C.** Change in allele frequency of polymorphic CpG sites identified within the three genes in the center of the Venn diagram in *A*. Allele frequencies are encoded to show the frequency of the allele that contains the CpG pattern at a particular site rather than the alternative allele.



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