

## Divergence and gene flow among Darwin's finches: A genome-wide view of adaptive radiation driven by interspecies allele sharing

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A recent analysis of the genomes of Darwin's finches revealed extensive interspecies allele sharing throughout the history of the radiation and identified a key locus responsible for morphological evolution in this group. The radiation of Darwin's finches on the Galápagos archipelago has long been regarded as an iconic study system for field ecology and evolutionary biology. Coupled with an extensive history of field work, these latest findings affirm the increasing acceptance of introgressive hybridization, or gene flow between species, as a significant contributor to adaptive evolution. Here, we review and discuss these findings in relation to both classical work on Darwin's finches and contemporary work showing similar evolutionary signatures in other biological systems. The continued unification of genomic data with field biology promises to further elucidate the molecular basis of adaptation in Darwin's finches and well beyond.

### Keywords:

■ adaptation; adaptive radiation; genomics; hybridization; introgression

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### Introduction

The fields of ecology, evolutionary biology, and animal behavior are deeply rooted in organismal natural history. For centuries, curious naturalists have observed and cataloged the spectacular biology of diverse plants and animals in their natural environment, and no natural historian is more famous than Charles Darwin, the founder of modern evolutionary theory. In developing his theory of evolution by natural selection, Darwin wove together many detailed observations of organismal biology to produce a compelling argument that left little room for doubt regarding his basic tenets of descent with modification and the power of natural selection to produce remarkable phenotypic adaptation [1, 2]. Today, as we continue to work out the ancestral relationships among taxa and explore the specific evolutionary processes responsible for adaptation, it is becoming increasingly clear that essential historical clues lie hidden in the genes that control organismal phenotypes [3–6]. However, the quest to find these genes is often an arduous one [7–10]. Genomics research, and the sub-fields of comparative and population genomics specifically, offers huge promise to unlock the molecular basis of biodiversity [11, 12]. With the rapid advance of genome sequencing technology, we appear to be entering a “golden age” for evolutionary genetics [11], one in which the hunt for genes underlying adaptation is progressing rapidly.

Recently, there have been a number of instances in which genomic approaches have produced major insights into classic evolutionary systems and questions, such as the diversification of cichlid [13] and stickleback [14] fishes, the evolution of mimicry in *Heliconius* butterflies [15], and the genetics of migration in the monarch butterfly [16]. A recent example of the power of population-level genomics to generate new understanding of an age-old question is a recent publication by Lamichhaney et al. [17] on Darwin's finches. Here, whole-genome sequencing of an entire adaptive radiation has been coupled with a study system that has an extensive record of field

research focused on natural history and ecology. The results reveal the history of diversification and gene flow among species as well as identify specific genes associated with an iconic morphological adaptation, beak shape. The findings also further unify observational evidence for interspecific hybridization with genetic evidence for adaptive interspecies allele sharing. This study, along with several other recent investigations [15, 18–20], reinforces the increasing acknowledgment of adaptive introgression as a potentially important and widespread evolutionary phenomenon.

## A tradition of field biology research on Darwin's finches

Darwin's finches are a group of about 14 species that evolved from a common ancestor on the Galápagos archipelago, a 15th species inhabiting Cocos Island (Fig. 1). Since Charles Darwin's voyage on the *HMS Beagle*, this radiation has been the focal point of novel insights into evolutionary biology. Darwin's observations of the finch radiation led him to develop foundational ideas about evolution, including descent from a common ancestor, island colonization by mainland species, and adaptive radiation [1]. It was years after the *Beagle* voyage, however, that Darwin received input on the group's morphological variation and systematics from taxonomist John Gould and formulated the insights for which he is famous [21]. Darwin became particularly drawn to beak shape, and noting the incredible diversity in this trait among

the closely related finches, he stated in the second edition of *Journal of Researches (Voyage of the Beagle)* [22] "Seeing this gradation and diversity of structure in one small, intimately related group of birds, one might really fancy that from an original paucity of birds in this archipelago, one species had been taken and modified for different ends." Darwin's statement here about the Galápagos finches, 14 years before *On the Origin of Species* [1], reveals the early emergence of his evolutionary thinking.

More recently, the detailed work of Peter and Rosemary Grant has established the connection between climatic fluctuation, seed availability, and natural selection on beak morphology [23–25]. Furthermore, their work also documented detailed observations of immigration and hybridization producing viable offspring [25–27]. Additional analyses of song revealed the directionality of gene flow from hybrids into the parental populations [28–30]. The synthesis of 40 years of observations combined with analyses of beak morphology and body size, song, and microsatellite genetic data showed convergent evolution in Darwin's finches owing to introgressive hybridization and natural selection [31, 32].

Advances by Podos, Huber, Hendry, DeLeón, and co-workers addressed the processes underlying adaptive radiation in Darwin's finches [33–36]. Podos [33] demonstrated that divergence in beak morphology drove evolution in vocal mating signals, likely promoting reproductive isolation and rapid speciation in the finch radiation. Huber et al. [34] found beak size polymorphism in a *Geospiza fortis* population on Santa Cruz island, presumably owing to ecological divergence, and subsequent assortative mating of the two morphs reminiscent of incipient speciation. Parallel studies related these findings to human impacts, showing how increased human population density can reduce the correlations between beak shape, size, bite force, and diet, thereby increasing the frequency of intermediate phenotypes and negatively impacting adaptive radiation [35, 36].

## Genetic insight on beak development reveals the developmental modules underlying morphological change

Previous work by Abzhanov and colleagues [37–39] has investigated the developmental genetics of beak variation among Darwin's finches. Two anatomical components, the prenasal cartilage (pnc) and premaxillary bone (pmx), determine adult beak morphology. One study compared embryonic pnc development of the six *Geospiza* finch species and analyzed expression patterns of candidate growth factor genes involved in avian craniofacial development [38]. This study found a correlation between earlier and spatially broader expression of *Bone morphogenetic protein 4* (*Bmp4*) in the developing upper beak and the deep, wide beak morphology of the ground finches [38]. *Bmp4*, however, was not implicated in the alternative elongated beak phenotype, suggesting the involvement of other genes [37]. To investigate the genetics of beak elongation, and go beyond candidate genes with a known role in craniofacial development, Abzhanov et al. [37] subsequently used a DNA microarray analysis. Using the sharp-beaked finch *Geospiza*



**Figure 1.** Representatives of the Darwin's finch radiation. Illustrations from *Birds Part 3 No. 4* (1839) and *Birds Part 3 No. 5* (1841) of *The zoology of the voyage of H.M.S. Beagle* by John Gould, edited by Charles Darwin. Reproduced with permission from John van Wyhe ed. 2002-. The Complete Work of Charles Darwin Online (<http://darwin-online.org.uk/>).

*difficilis* as a reference, transcripts up-regulated in the long-beaked cactus finches were distinguished from transcripts that were down-regulated or whose expression remained unchanged in the ground finches [37]. This approach revealed *Calmodulin* (*CaM*), a  $Ca^{2+}$  binding protein involved in  $Ca^{2+}$ -dependent signal transduction, as a top candidate for beak morphogenesis. Further experiments misexpressing *CaM* in chick embryos produced the expected elongated beak phenotype [37]. Together, these studies suggested a modular developmental genetic basis for variation in *pnc*-determined beak morphology in which *Bmp4* regulates depth and width, and *CaM* acts on the length axis. A complementary study that focused on *pmx* development in the ground finches used the same microarray screen to reveal three candidate genes for *pmx* patterning: *TGFβ receptor type II* (*TGFβIIr*), *β-catenin*, and *Dickkopf-3* (*Dkk3*) [39]. Further analysis showed that domains of expression of these candidate genes correlated with adult morphology and that the genes interact to determine different axes of growth [39].

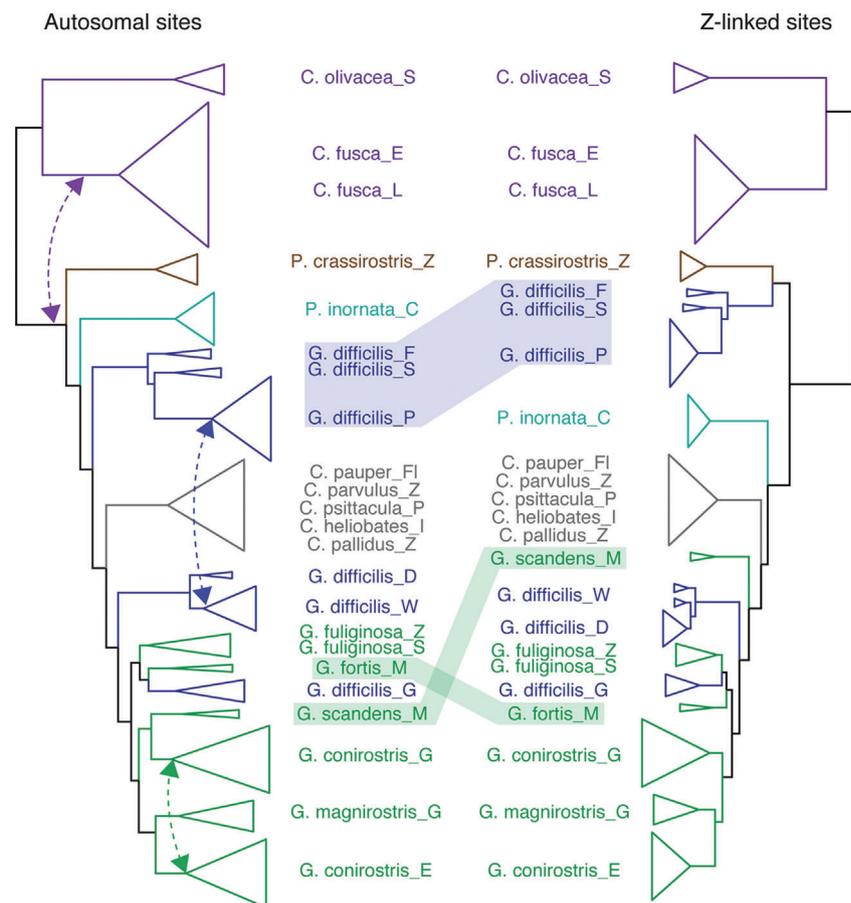
Prior to Lamichhaney et al.'s comprehensive genomic analysis [17], two Darwin's finch genomes had been sequenced. In 2012, the genome of a female medium ground finch, *G. fortis* was published [40] as part of a suite of avian genomes [41–43]. In 2013, Rands et al. [44] published the genome of *G. magnirostris* and analyzed it in comparison to other vertebrates; zebra finch and *G. fortis* in particular. An analysis of positive selection by Rands et al. [44], based on patterns of synonymous and non-synonymous substitutions in a filtered set of 1,452 orthologs, yielded 21 genes with putatively adaptive amino acid substitutions in the Darwin's finch lineage. At least two of these genes, *POU1F1* and *IGF2R*, have been implicated in craniofacial development, suggesting a potential role in beak morphogenesis.

## Integrating genomics of adaptive radiation and field biology

In the latest advance in this historic tale, Lamichhaney et al. [17] present an expanded genomic approach toward understanding the evolutionary history of Darwin's finches. They sequence 120 full genomes, representing all the species in the Darwin's finch radiation and incorporating populations from multiple islands, and two closely related tanagers, *Tiaris bicolor* and *Loxigilla noctis*. Analyses of this dataset reveal some striking patterns. First, in concordance with prior observations reporting inter-species hybridization and migration

between islands, whole-genome comparisons between species reveal high genetic diversity and extensive sharing of genetic variation, especially between ground and tree finches. The autosomal genome-based phylogenetic tree dates the birth of the radiation to circa 900,000 years ago and the radiation of ground and tree finches to 100,000–300,000 years ago. This tree topology generally supports the classical taxonomy based on mtDNA and morphology [45–47], with warbler finches as the first group to branch off and the ground and tree finches as the crown group. However, the phylogeny reveals two polyphyletic species, *G. difficilis* (also reported in [45]) and *G. conirostris*, which depart from the existing taxonomy. *G. difficilis*, which occurs on six islands, is split into three groups, and *G. conirostris* is split into two groups (Fig. 2). The polyphyletic groupings of both species are associated with taxon sampling from multiple islands, emphasizing the importance of geography in the branching order of recently evolved groups.

Lamichhaney et al. attribute allele sharing between species to introgressive hybridization via multiple lines of evidence, including ABBA-BABA tests [48, 49] and



**Figure 2.** Maximum-likelihood phylogenies of Darwin's finches. Dashed arrows indicate gene flow between species. Highlighted bars denote key discordances between the trees. Branches ending with triangles indicate multiple genomes. Letters after species names indicate island sampled: S, Santiago; E, Española; L, San Cristóbal; Z, Santa Cruz; F, Fernandina; C, Cocos; P, Pinta; FI, Floreana; I, Isabela; M, Daphne; D, Darwin; W, Wolf; G, Genovesa.

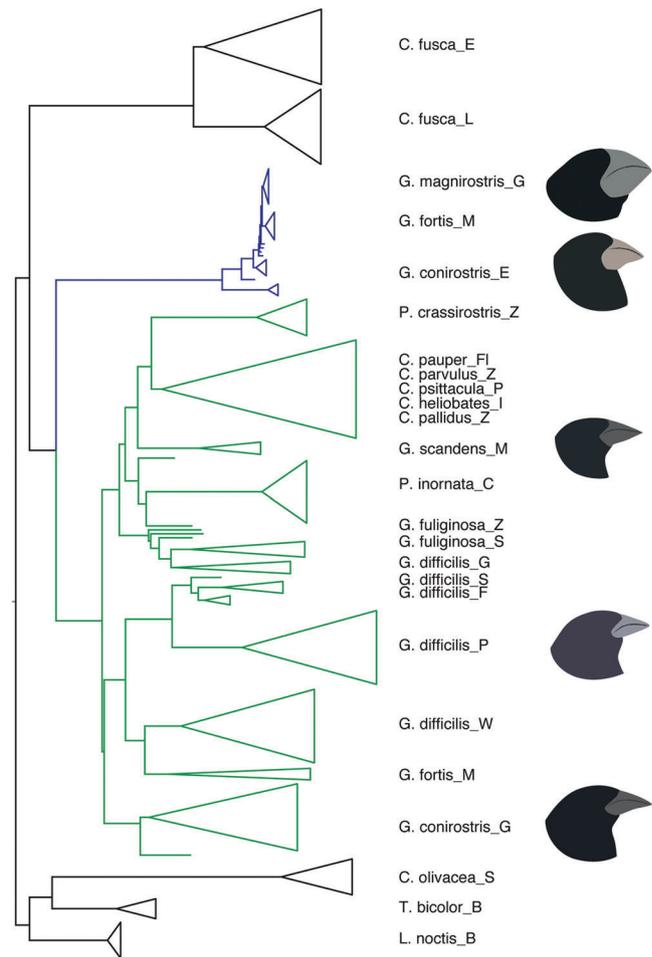
discordance between autosomal and sex-linked phylogenetic tree topologies (Fig. 2). ABBA-BABA tests show that despite a closer genetic relationship to *G. magnirostris* on Genovesa, *G. difficilis* on Wolf shares alleles with *G. difficilis* on Pinta. Another ABBA-BABA comparison confirms the proximate genetic relationship of *G. magnirostris* on Genovesa and *G. conirostris* on Española, but also shows gene flow between *G. conirostris* on Española and *G. conirostris* on Genovesa. Introgression of loci affecting phenotypic characters could explain the similarities upon which the two *G. difficilis* populations and the two *G. conirostris* populations were grouped in the classical taxonomy. In addition to these cases of recent introgressive hybridization, the authors find ABBA-BABA support for gene flow between the warbler finch *C. fusca* and the common ancestor of the non-warbler finches.

Sex-linked genes are well known to play a large role in speciation, and hence these loci generally show less interspecific gene flow in comparison to autosomal loci [50]. The discordance between the autosomal and sex-linked tree topologies for Darwin's finches, particularly with respect to the placement of *G. difficilis* from Pinta, Fernandina, and Santiago, supports the hypothesis of gene flow between this group and the ground and tree finches after the split of the Cocos finch. Phylogenies based on mtDNA and W-linked loci also support this interpretation. In addition, a separate analysis of demographic history within the group shows a large effective population size among the ground finches in comparison to the other taxa, consistent with gene flow among ground finch species.

To explore the genetic architecture of beak shape variation, Lamichhaney et al. perform a genome-wide scan of genetic differentiation ( $ZF_{ST}$ ) on 15 kb (kilobase) windows between two groups of closely related finches distinguished by having blunt (*G. magnirostris* from Genovesa and *G. conirostris* from Española) or pointed (*G. conirostris* from Genovesa and *G. difficilis* from Wolf) beaks. A number of genomic regions emerge from this analysis, many of which house genes with potential roles in beak development. The highest scoring window contains the gene *ALX homeobox 1* (*ALX1*), which is known to play a central role in vertebrate craniofacial development [51, 52]. A phylogenetic tree of Darwin's finches based on the *ALX1* region groups individuals into two clades based on their blunt versus pointed beak morphology (Fig. 3). The divergence between blunt and pointed haplotypes is inferred to be quite old, having occurred soon after the split of the warbler finches and other Darwin's finches. The medium ground finch, *G. fortis*, a species that varies in beak shape on Daphne Major, is also polymorphic for these highly divergent *ALX1* haplotypes, and SNP genotyping of *G. fortis* specimens from this island reveals a significant association between the *ALX1* locus and blunt versus pointed beak morphology.

## Introgression and adaptation

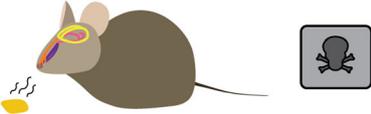
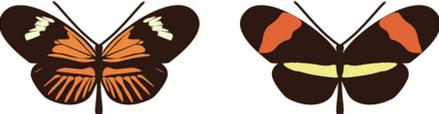
Genomic studies in various systems have uncovered evidence for adaptive allele sharing between closely related species, apparently as a result of introgression [53–60], and several of these investigations point to the exchange of distinct phenotypic traits (Fig. 4). For instance, mosquitoes in the



**Figure 3.** Haplotype tree of beak shape locus *ALX1*. Neighbor-joining tree based on *ALX1* reveals a deep split between blunt and pointed beak haplotypes. Representative finch heads reflect species grouping by beak morphology as opposed to historical branching order. Branches ending with triangles indicate multiple *ALX1* haplotype sequences.

*Anopheles gambiae* complex have experienced such extensive interspecific gene flow that most of the genome no longer reflects the history of species-level diversification [18], and traits such as desiccation resistance and insecticide resistance have been transferred between species as a result [61–63]. Similarly, the house mouse, *Mus musculus domesticus*, has experienced substantial gene flow from the Algerian mouse, *Mus spretus* [20], resulting in introgression of alleles at olfactory receptors [20] as well as rodenticide resistance [64]. *Heliconius* butterflies have a long history of divergence with gene flow [65] and haplotypes at two major loci controlling wing patterning have been transferred among groups of closely related species as a result of natural selection for mimicry [15, 66]. Even modern humans have benefited from introgression: a haplotype at the hypoxia pathway gene *EPAS1*, associated with high-altitude hemoglobin concentration in Tibetans, appears to have been acquired from a Denisovan-like archaic human lineage [19].

It is important to note, however, that two distinct evolutionary processes can produce similar patterns of

Adaptation	Reference
	Darwin's finches: beak shape variation Lamichhaney <i>et al.</i> , 2015
	<i>Anopheles</i> : insecticide resistance, desiccation resistance Fontaine <i>et al.</i> , 2015 Norris <i>et al.</i> , 2015 Fouet <i>et al.</i> , 2012 Gray <i>et al.</i> , 2009
	<i>Mus</i> : olfactory receptors, rodenticide resistance Liu <i>et al.</i> , 2015 Song <i>et al.</i> , 2011
	<i>Heliconius</i> : wing pattern mimicry The <i>Heliconius</i> Genome Consortium, 2012 Pardo-Diaz <i>et al.</i> , 2012
	Humans: high altitude adaptation Huerta-Sánchez <i>et al.</i> , 2014

**Figure 4.** Summary of recent studies of adaptive introgression in animals. Examples highlight the exchange of distinct adaptive phenotypic traits between species.

shared ancestry at focal regions of the genome: introgression and incomplete lineage sorting (ILS) of ancestral variation. For instance, in the case of the finches, it is possible that because the blunt and pointed *ALX1* haplotypes diverged long ago, prior to much of the species-level diversification, this may be a long-standing polymorphism that has sorted out over time, resulting in some species becoming fixed for one ancient haplotype (blunt) and other species becoming fixed for the other ancient haplotype (pointed). Under this scenario, species share similar sequences today and group by phenotype on the *ALX1* tree as a result of ILS, not introgression. Work in *Anopheles* [18], *Mus* [20], *Heliconius* [67], and humans [19] has explicitly considered ILS as an alternative explanation to introgression at target loci and the data from these systems generally support the introgression hypothesis. Overall, Lamichhaney *et al.* present compelling genome-wide evidence for a history of divergence with gene flow among Darwin's finches and remarkable allele sharing at a locus responsible for phenotypic diversity and adaptation. In terms of *ALX1* specifically, some patterns in the data, such as the very short branch lengths among blunt haplotype sequences on the *ALX1* tree, are definitely consistent with introgression (and selection). In contrast, the relatively long branch lengths among pointed haplotype sequences, and the fact that the *G. fortis* sequences do not group with *G. scandens* and *G. fuliginosa*, putative donor

species [17], may suggest a potential role for ancestral variation as well. Future work including expanded sampling and sequencing of *G. fortis* from Daphne Major, and analyses of DNA sequence divergence and ABBA-BABA patterns of allele sharing among putatively introgressed *ALX1* haplotypes will help clarify this history.

## Conclusions and outlook

Lamichhaney *et al.*'s discovery of *ALX1* raises many fascinating questions. For instance, what is the ultimate source of the two highly divergent, blunt and pointed haplotypes? The authors detect a genome-wide signature of ancient introgression between *C. fusca* and the common ancestor of the non-warbler finches, which may indicate that ancient hybridization contributed some of the critical genetic variation – perhaps one of these *ALX1* haplotypes even – that originally fueled the finch radiation on the Galápagos. Furthermore, Lamichhaney *et al.* present evidence that these two haplotypes frequently occur together in heterozygotes, both in interspecific hybrids and in polymorphic species such as *G. fortis*. However, based on the sequence data presented, the two haplotypes do not appear to recombine. This may suggest that structural variation, like a chromosomal inversion polymorphism, is maintaining alternate copies. By reducing

recombination between loci, inversions can maintain linkage between co-adapted alleles and this can have profound impacts on adaptation and speciation [68–70]. Moving beyond *ALX1*, it will be fascinating to explore the evolution of the many other genes that emerged from the genome-wide comparison between finches with blunt and pointed beaks. Given that birds with differing beak morphology are also likely to differ in other aspects of their biology, a detailed analysis of these genes and their evolutionary histories is almost certain to yield insights far beyond beak development.

Finally, we must note that it is not only the incredible dataset, sophisticated analyses, and discovery of *ALX1* that make this most recent study of Darwin's finches so remarkable, but the integration of these new insights with detailed knowledge collected over decades about the ecology and evolutionary history of the study system. Genome sequencing technology will continue to advance and the application of these tools will proceed virtually without limit, but the biological context in which we interpret these genomic data is irreplaceable. In our modern exploration of evolutionary biology, natural history and ecology are essential counterparts to genomics because they enable us to establish direct connections between sequence variation and natural selection. For this reason, Darwin's finches have been providing critical insight into the evolutionary process for over 150 years and it seems that they still have plenty more to tell us.

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