

GENOME EVOLUTION AND SPECIATION: TOWARD QUANTITATIVE DESCRIPTIONS OF PATTERN AND PROCESS

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Studies of patterns of differentiation across genomes are accumulating, yet integrative work that combines approaches and fully capitalizes on new technologies to test explicit hypotheses is still rare. Thus, debates persist about the rate, magnitude, and causes of genomic change. This special section is devoted to helping resolve these debates. The eight studies contained within demonstrate how we can begin to move away from vague metaphors toward quantitative and more precise descriptors of patterns of genetic architecture and divergence. However, a particular genomic pattern can often arise via different combinations of various processes such as selection, gene flow, recombination, mutation, genetic drift, and demographic variability. Thus, substantial challenges remain in elucidating which evolutionary processes generated observed genomic patterns. Nonetheless, the studies in this section demonstrate ways forward toward bridging pattern and process, including experimental work, genetic mapping, increased knowledge of natural history and demography, and comparative studies spanning taxa at different points in the speciation continuum. Such collective work will lead to more powerful hypothesis testing. Future work can also help better integrate the contributions of ecology, genome structure (e.g., inversions and translocations), and genetic conflict to genome evolution.

KEY WORDS: Adaptation, genetic architecture, genomic divergence, next-generation sequencing, population genomics, speciation.

A major goal in biology is to understand evolution at a genome-wide level. New sequencing technologies are revolutionizing the study of genomic variability and population divergence (Margulies et al. 2005; Ellegren 2008). Nonetheless, the field of population genomics is still in its infancy and few studies have yet combined complementary approaches to fully capitalize on new technologies and test explicit hypotheses. Thus, a number of debates persist about the roles that different processes play in generating genomic divergence (Noor and Bennett 2009; Barrett and Hoekstra 2011), the proportion of the genome affected by

natural selection and how strongly so (Kimura 1979), the size and distribution of genomic regions of differentiation (Via 2009, 2012), and the rate and frequency of genomic changes. The papers in this special section begin to address these issues and, as we discuss later, yield a number of insights (Table 1).

Numerous past reviews of genomic divergence exist (Nielsen 2005; Stinchcombe and Hoekstra 2008; Butlin 2010), including articles by us (Nosil et al. 2009a; Feder et al. 2012; Nosil and Feder 2012). Thus, our goal here is not to provide a broad review of the topic. Rather, we highlight how our understanding

Table 1. Summary of the studies in the special section, the data they considered, some (but not all) of the main results, and associated implications. The coverage of findings and implications is meant to be illustrative rather than complete.

Organism	Data	Some main results	One implication	Reference
<i>Lycacoides</i> butterflies	GBS-based genome scan coupled with introgression analyses and genome wide association mapping of phenotypic traits	A modest number of SNPs contributed to trait variation and these SNPs were sometimes, but not always, highly divergent between species	Phenotypic divergence sometimes but not always contributes to genomic divergence and speciation	(Gompert et al. 2013)
<i>Rhagoletis</i> fruit flies	Microsatellite-based genome scan coupled with linkage mapping	For the same set of loci, levels of divergence across the genome between host races were correlated with that between species, but with species exhibiting larger absolute divergence	Similar regions are affected by selection across different points of the speciation continuum and species appear to be host-races “writ large”	(Powell et al. 2013)
<i>Helianthus</i> sunflowers	GBS-based genome scan coupled with draft whole genome assembly	Major regions of divergence were few and large between an ecotype pair within species, but more numerous, smaller, and more widespread between a species pair	Dynamics of genomic divergence within vs. between species differ	(Andrew and Rieseberg 2013)
<i>Coregonus</i> whitefish	GBS-based genome scan coupled with linkage mapping and linkage disequilibrium (LD) analyses	The size, but not number, of genomic regions of accentuated divergence, and associated strength of barriers to gene flow and degree of LD, varied among five ecotype pairs according to degree of phenotypic differentiation	Genomic divergence builds up with, and is promoted by, phenotypic differentiation	(Gagnaire et al. 2013)
<i>Mimulus</i> mon-keyflowers	Comparative linkage mapping and quantitative trait locus (QTL) mapping	Regions harboring QTL for floral traits and hybrid sterility mapped to regions of lower effective recombination in hybrids, suggesting possible structural differences between species (inversions and translocations)	Reduced recombination promotes phenotypic divergence and speciation	(Fishman et al. 2013)
<i>Gasterosteus</i> stickleback	Microsatellite-based genome scan using both nongenic loci (“neutral markers”) and those linked to candidate genes (“adaptive markers”)	Divergence in adaptive markers correlated with differences in salinity and although selection appeared to act strongly only on those regions, a correlation between adaptive and neutral markers was nonetheless detected	Divergent selection related to ecological differences promotes both neutral and adaptive genetic divergence	(DeFaveri et al. 2013)
<i>Senecio</i> groundsel	GBS-based genome scan coupled with functional annotation of divergent regions	Divergence followed complex genetic trajectories, affecting a significant fraction of the genome and implying both the parallel recruitment of the same alleles and the divergence of completely different genomic regions across geography	Evolution repeated itself, but with somewhat different genetic underpinnings in different populations	(Roda et al. 2013)
Mathematical model	Computer simulations examining the role of direct selection and different forms on hitchhiking on the dynamic build up of genomic divergence and reproductive isolation over time	Genetic hitchhiking aided the buildup of genomic divergence above that observed under direct selection alone, but the role of physical linkage was limited (i.e., selection on unlinked loci could reduce average genome wide gene flow, promoting genetic divergence, via “genome hitchhiking”)	Genome hitchhiking promotes reproductive isolation and is important for genome wide “congealing” or “coupling” of differentiation (F_{ST}) across loci as speciation progresses	(Flaxman et al. 2013)

GBS = genotype-by-sequencing (generally yields SNPs, single nucleotide polymorphisms).

of the connections between genomic patterns and evolutionary processes while improving, is still incomplete. We then synthesize how the articles in this special section begin to fill this gap in our knowledge, focusing on three main themes: (1) our ability to now quantify patterns of genomic divergence with higher resolution; (2) difficulties and progress in connecting pattern and process; and (3) discerning how divergence unfolds over time.

Genome Wide Patterns

Prior to the advent of next-generation sequencing, descriptions of patterns of genomic divergence were generally crude relative to what is possible now, and thus even qualitative descriptions of genomic patterns served useful purposes. In contrast, we can now obtain fine scale resolution in our descriptions of genomic divergence for numerous individuals and populations. This has led to increased appreciation of the complexities of genomic divergence and how multiple processes can interact to generate observed patterns. For example, both stronger selection and reduced recombination might contribute to genetic differentiation between populations diverging in the face of gene flow (Felsenstein 1981; Feder et al. 2012). Thus, metaphors such as “genomic islands of divergence” (which we have frequently used ourselves, e.g., Nosil et al. 2009a; Feder and Nosil 2010; Michel et al. 2010) that initially served as convenient descriptors of pattern are rather vague and less useful for resolving underlying process. More quantitative and precise dissection of genomic patterns, and terminology, is now required to push the field forward, as exemplified by studies in this special section.

For example, four studies in this section considered thousands or more single nucleotide polymorphisms (SNPs) obtained from next generation genotyping-by-sequencing methods to survey genome wide patterns of genetic differentiation (Andrew and Rieseberg 2013; Gagnaire et al. 2013; Gompert et al. 2013; Roda et al. 2013). All these genome scans detected strong heterogeneity in levels of population differentiation among genomic regions and three also used genetic or physical map information to consider the distribution of divergence across the genome. However, details of their findings varied. For example, in a study of hybridizing *Helianthus* sunflowers, Andrew and Rieseberg 2013 reported that major regions of divergence were few, clustered, and large between ecotypes within species, but were more numerous, smaller, and genomically widespread between a sympatric species pair (see original study for quantitative details). In contrast to the results with sunflowers, a genome scan of *Coregonus* whitefish ecotypes found that although the magnitude of divergence increased genome-wide with greater phenotypic differences between ecotypes, the overall number of regions showing exceptional differentiation was similar among

different ecotype pairs (Gagnaire et al. 2013). These studies highlight how much work remains to be done in characterizing patterns of genomic divergence to discern if general rules exist.

Other studies in the special section adopted different approaches. For example, DeFaveri et al. (2013) used directed contrasts of divergence at loci linked to candidate genes versus non-genic loci (rather than random genome wide surveys) in oceanic *Gasterosteus* stickleback and report that both regions affected by selection and putatively neutrally evolving regions varied according to environmental conditions (e.g., salinity). All of the above studies provide quantitative estimates of patterns of genomic divergence. Eventually such surveys of numerous genomic regions will be extended to the base pair level resolution, for example using whole genome resequencing (e.g., Ellegren et al. 2012; Jones et al. 2012), and further integrated with genetic and physical maps. In addition, by examining numerous individuals and sometimes multiple populations, the studies in this special section illustrate how properly quantifying population-level parameters will require population-level samples (i.e., genomic data from more than just a few individuals).

Processes Driving Divergence

A major remaining challenge is to connect the deluge of data providing ever broader and finer scale descriptions of genomic patterns of differentiation to the evolutionary processes generating them. With the exception of a few laboratory experiments (Barrick et al. 2009; Burke et al. 2010; Paterson et al. 2010; Fournier-Level et al. 2011), most genomic studies rely on observational descriptions of patterns of divergence, and often only from a single source of data (e.g., genome scans without reference to quantitative trait loci [QTL], gene expression differences, etc.). Nevertheless, these population genomic studies have usefully identified loci exhibiting exceptional levels of genomic divergence. However, it can be problematic to use these results alone to infer evolutionary process because a particular genomic pattern can often arise via different combinations of multiple processes such as selection, recombination, drift, gene flow, mutation, and demographic variability (Nielsen 2005; McGaugh and Noor 2012b; Nachman and Payseur 2012a). In turn, this makes it difficult to specify an appropriate neutral model for observational data, complicating inference of departures from selective neutrality. Moreover, even the process of selection can involve multiple factors such as ecological divergence, reinforcement, and sexual selection (Nosil et al. 2012a).

In short, the field of genomics is yet to enter a truly integrative and experimental phase where multiple sources of complementary data and experiments are used to directly disentangle the causes and consequences of genome evolution (Fig. 1). The articles contained in this issue show how we can begin to do so. For

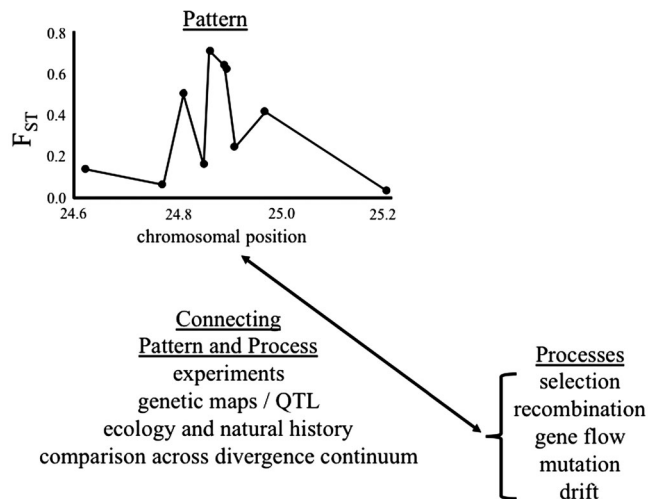


Figure 1. A given genomic pattern can be generated via different combinations of multiple evolutionary processes. A number of approaches, including manipulative transplant and selection experiments, when coupled with genome scans for differentiation, can help better connect pattern and process.

example, the study of threespine stickleback by DeFaveri et al. (2013) combined ecological and genetic data to show that the process of natural selection was likely reducing gene flow across the genome strongly enough to result in general associations between genetic distance and the degree of ecological divergence (“isolation-by-adaptation” cf. Nosil et al. 2008, 2009a). Roda et al. (2013) combined a genome scan of a flowering plant with ecological data and functional annotation to demonstrate that adaptation to coastal environments occurred, at least in part, through the recruitment of different alleles in different populations and even different genes participating in similar processes. The integrative study by Gompert et al. (2013) combined the results of a genome scan of divergence between hybridizing *Lycaeides* butterflies with new data from genome wide association mapping of phenotypic traits putatively involved in reproductive isolation. This allowed a test of the extent to which gene regions associated with phenotypic traits also exhibit strong differentiation in nature, as expected if the process of natural selection promotes genomic divergence (see also Nosil et al. 2012b). The authors used a recently developed multilocus method of mapping (Guan and Stephens 2011) that has advantages over typical single SNP-by-SNP methods, for example being able to quantitatively describe genetic architecture parameters such as the number of SNPs contribution to trait variation and their effect sizes, and estimate uncertainty in these parameters. The results revealed that a modest number of SNPs were associated with trait variation and that these sometimes, but not always, exhibited accentuated genetic divergence between species.

Another process warranting consideration is recombination, because theory predicts that reduced recombination can facilitate genomic divergence (Noor et al. 2001; Rieseberg 2001; Navarro and Barton 2003; Kirkpatrick and Barton 2006; Hoffmann and Rieseberg 2008; Feder and Nosil 2009; Feder et al. 2011; Nachman and Payseur 2012b). Here, studies considering structural features of the genome that reduce recombination, such as chromosomal inversions, are of interest. Fishman et al. (2013) provide evidence from reduced effective recombination of some gene regions that structural differences, possibly including inversions and translocations, may distinguish species of *Mimulus* monkeyflowers. Consistent with a role for such features in speciation and genetic divergence, traits such as floral morphology and hybrid sterility largely map to the regions exhibiting structural variability. However, additional karyotype and mapping data demonstrating reversed gene order are needed to confirm a role for inversions. A role for structural variation is also reported for *Rhagoletis* flies, where accentuated genetic divergence of regions harboring chromosomal inversions between host races was observed between both host races and a species pair (Powell et al. 2013). Finally, the study of *Helianthus* sunflowers documented that regions of accentuated genetic divergence were in areas of high marker density, consistent with reduced recombination in these regions (Andrew and Rieseberg 2013). These studies add to a growing body of empirical studies implicating reduced recombination in speciation (Kitano et al. 2009; Strasburg et al. 2009; Lowry and Willis 2010; Michel et al. 2010; Joron et al. 2011; Jones et al. 2012; McGaugh and Noor 2012a; Nachman and Payseur 2012b).

Collectively, the work described earlier demonstrates how integrative studies can begin to isolate the contribution of different processes to genomic divergence. Thus, future work in general might extend high-resolution genome scans such as those recently published not only in this issue but in other studies of stickleback, mosquitoes, butterflies, and birds (Lawniczak et al. 2010; Ellegren et al. 2012; Heliconius Genome 2012; Jones et al. 2012) to test whether differentiation reflects a balance between the diversifying versus constraining effects of various evolutionary processes. In particular, in addition to selection and recombination, the roles of gene flow, mutation, standing genetic variation, and effective population size warrant consideration.

The Speciation Continuum

An additional difficulty with studying the genomics of speciation is that population divergence and speciation unfolds over time, and usually over timescales that are too long to study directly. Thus, our understanding of the genomic basis of speciation will benefit from replicated studies of closely related taxa that span a range of divergence across the ‘speciation continuum’ (Nosil

et al. 2009b). Such studies might thus allow us to reconstruct how genomic divergence unfolds as speciation proceeds through time. However, it must always be remembered that such studies are ‘reconstructions’ in the sense that they generally do not trace divergence and progression toward speciation in a single lineage through time. Rather they represent comparisons among related taxa that have reached different stages of the divergence process, with the inference that a single lineage would follow this course through time as speciation occurs (i.e., a ‘connect the dots’ approach, although note that experimental evolution with short-lived organisms could be used to achieve true time-slices). Although studies of the speciation continuum considering phenotypic divergence are increasing (Mallet et al. 2007; Mallet 2008; Berner et al. 2009; Hendry et al. 2009; Nosil and Harmon 2009; Peccoud et al. 2009; Merrill et al. 2011), genomic studies across the speciation continuum are still relatively rare.

Once again, studies in this special section begin to fill this gap. For example, Powell et al. (2013) examined genetic divergence across the same loci for both a host race pair within species and a species pair of *Rhagoletis* fruit flies: the apple and hawthorn races of *R. pomonella* versus their immediate sister taxon attacking *Cornus florida* (flowering dogwood). They report a significant correlation in genomic change among gene regions across this transition in the speciation continuum; regions of accentuated divergence between the host races are more strongly diverged for the sister species, with a few additional regions showing elevated differentiation in the flowering dogwood fly as well. This implies mostly similar regions are affected by selection at different points in the speciation process. Absolute levels of genetic divergence were greater between species, indicating that species may simply be host races “writ large,” differing in degree but not in kind from one another. In contrast, the opposing patterns of genomic divergence for ecotype versus species pairs of sunflowers described above indicate the dynamics of genomic divergence varies across the speciation process in this system (Andrew and Rieseberg 2013). One weakness of these two studies is that they examined only two points in the speciation process. The study by Gagnaire et al. (2013) examined five pairs of whitefish ecotypes to show that the size of genomic regions of accentuated divergence, and associated strength of barriers to gene flow, increased quantitatively with the degree of phenotypic differentiation between ecotypes. Collectively, these three studies expand the previously small number of published articles on genomic divergence across the speciation continuum (e.g., Heliconius Genome 2012; Nadeau et al. 2012).

Finally, considerations of the speciation continuum might especially benefit from theoretical modeling, which can more readily examine a range of time scales than empirical work and follow them through a single lineage “in silico.” When it comes to the processes promoting genomic divergence, there can be roles for

direct selection on a locus and two forms of genetic hitchhiking: (1) “divergence hitchhiking” (DH hereafter) due to local reductions in gene flow for regions physically linked to those under divergent selection; and (2) “genome hitchhiking” (GH hereafter) due more genome wide reductions in average gene flow generated by selection. Past theoretical investigations of DH and GH focused on static snapshots of divergence at one point in time. Flaxman et al. (2013) used computer simulations to investigate the relative importance of direct selection, GH, and DH in facilitating the dynamic buildup of genomic divergence as speciation proceeded through time. They found that hitchhiking could greatly aid the establishment of new mutations and genomic divergence, but that physical linkage (DH) generally provided little additional help relative to GH. Thus, GH promoted reproductive isolation by reducing effective migration rates below that due to direct selection alone, and was important for genome wide “congealing” or “coupling” of differentiation (F_{ST}) across loci as speciation progressed. These results suggest that selection on multiple unlinked loci can help drive the transition from populations to races to species via the effects of genome hitchhiking on reducing effective gene flow from a local scale around individual genes to a more collective, whole genome level.

FUTURE PROSPECTS

The studies in this special section demonstrate how the processes affecting patterns of genomic divergence can begin to be inferred in studies of adaptation and the speciation continuum. Nonetheless, a large number of issues remain unresolved. For example, we need more standardized and precise descriptors of genomic divergence and genetic architecture if we are to begin making comparisons among study systems. Another major consideration is the geography of speciation, not only whether it occurred with gene flow, but also whether gene flow was primary or secondary in nature. This is a difficult question to tackle, but an important one because secondary contact may sometimes result in different patterns of differentiation than in situ primary divergence, whereas at other times generate similar patterns. Moreover, in cases of secondary contact, gene flow and introgression should be confirmed by independent means, and not just inferred from heterogeneity in the pattern of genomic divergence, which can arise due to processes other than variation among loci in level of gene flow (Noor and Bennett 2009). Most work to date on genomic divergence has focused primarily on ecological factors or on structural considerations, but not both. In addition, potential effects of forms of intragenomic conflict, such as meiotic drive, on genome wide patterns are underexplored (Crespi and Nosil 2012). Future work could better integrate ecological, structural, and conflict-oriented aspects of genomic divergence.

Finally, the study of genomic divergence is yet to enter a truly experimental phase where transplant manipulations and

controlled selection experiments are used in concert with population surveys to isolate the factors both driving and constraining genomic divergence. For example, experiments focused on allele frequency changes within a generation can isolate the roles of selection and drift in driving change, because factors such as recombination, mutation, and biased gene conversion do not occur within generations. Although much remains to be learned, the studies contained in this issue show how we are making progress toward connecting patterns of genomic differentiation with their underlying causes, illuminating the evolutionary processes generating new species and biodiversity. In addition, the studies demonstrate that the tools are now available for continuing to make progress on a previously unprecedented scale.

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