Listening to Genetic Background Noise
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Since the early days of modern genetics, researchers have largely shut their ears to the “background noise” of genetic modifiers that modulate the expression of mendelian traits. Because modifier genes complicate regular patterns of inheritance and because their identification can be difficult, their importance has been recognized, but they have rarely been the focus of genetic studies. However, attention is beginning to focus on these genetic background effects, in part because they are the entry into the genetics and systems biology of more complex and common diseases, and in part because they have great potential as powerful and effective ways to treat and perhaps prevent disease.

Keeping things simple was the key to discovering the rules of inheritance. With insight and luck, Mendel carefully selected traits, emphasizing those that showed a virtually invariant phenotype. His crosses provided segregation ratios for these traits, from which the fundamental and universal rules of inheritance were inferred. Mendel’s landmark discovery would have been impossible if he, like others before him, had selected traits that show more complex patterns of inheritance. And yet, remarkably few traits are truly mendelian.

Most traits vary, sometimes in simple ways and sometimes in profound ways. Perhaps the most important discovery from the study of spontaneous, engineered, and chemically induced genetic variants in model organisms such as laboratory mice is that their phenotypes depend strongly on the genetic background. For example, a specific genetic variant may lead to embryonic lethality on some genetic backgrounds but to full viability and no obvious phenotype on other backgrounds. Background genes that can suppress or exacerbate detrimental phenotypes are ubiquitous and highly polymorphic. They are easiest to detect when a single genetic variant is the target of modification, but they are probably involved in both genetically simple and complex traits.

In general, phenotypic noise may result from allelic heterogeneity, variable environments, or stochastic effects, as well as from modifier genes. In humans, distinguishing among these sources of variability can be difficult. With model organisms, however, defined crosses can be made, so detecting modifiers is relatively easy. Moreover, because the repertoire of genes in humans is extraordinarily similar to that in other mammals and because the chromosomal arrangement of these genes has been strongly conserved during mammalian evolution, the identity and location of candidate modifier genes in humans can be reliably predicted from studies in model organisms.

Modifier genes are now leading to pioneering discoveries about the genetics and biology of hearing. In a study in this issue of the Journal, Schultz et al.1 show that five members of a family with autosomal recessive sensorineural hearing loss were homozygous for a missense mutation at a conserved site in CDH23, the gene that encodes cadherin 23, which mediates calcium-dependent cell-to-cell interactions. Mutations in this gene have previously been shown to cause a similar form of hearing loss in waltzer mice.2 The authors also note that three of the five affected persons had severe-to-profound hearing loss, whereas the other two had only high-frequency sensorineural hearing loss. This variability suggested the action of a modifier gene. Again, studies in mice pointed the way. Variants of the Atp2b2 gene, which encodes a calcium pump in the plasma membrane, modulate the severity of hearing loss in waltzer mice. Schultz et al. report that heterozygosity for a missense mutation in ATP2B2, the human homologue of Atp2b2, was associated with the severity of hearing loss in these five persons. During the study, they speculated that variation in the activity of the calcium pump influences cellular interactions that depend on calcium availability. They then tested whether this ATP2B2 variant modifies other forms of hearing loss and found that it affected hearing loss resulting from other genetic causes. Interestingly, heterozygosity for the ATP2B2 variant was not sufficient to cause hearing loss — an observation that is typical of most modifier genes: in the absence of their target gene variants, they generally do not have detectable effects on the trait. These discoveries about the genetic basis of sensorineural hearing loss in humans would have been much more difficult had there not been corresponding discoveries in mice to guide the way. This cross-talk between studies in humans and those in model organisms is probably essential for rapid progress.

Modifier genes complicate the genetics of sim-
ple traits and simplify the genetics of complex traits. Genetic variants differ in the magnitude of their effects (a phenomenon called “effect size”). Effect sizes range from simple mendelian traits, in which differences at a single gene account for all the phenotypic variation in a trait, to the other extreme, where a large number of genes with individually small effects control phenotypic variability. Modifier genes reduce the effects attributable to the mendelian variant that is the target of modification and increase those attributable to the modifier gene. As the number of modifier genes and the cumulative magnitude of their influence increase, the effect size of a single gene diminishes and genetic complexity increases. But just as they reduce the effects of genes associated with simple traits, modifier genes increase the influence of genes with subtle effects. In mouse models of diseases such as testicular cancer, modifier genes have been used to magnify genetic effects, rendering them amenable to analysis.

The considerable polymorphism of modifier genes is puzzling. If modifier effects are beneficial, why are they polymorphic, rather than fixed, such that all the members of a population might have the advantage of their beneficial effects? Presumably, the myriad ways that modifiers interact with many genetic variants mean that no single variant is universally beneficial. Instead, their polymorphism probably reflects the ongoing response of organisms to diverse genetic and environmental perturbations during the lifetime of an individual and the lifetime of the species. In other words, polymorphic challenges require polymorphic responses.

Modifier genes are evidence of the adaptive response of organisms to genetic and environmental perturbations. Every organism carries new and inherited mutations that adversely affect viability and fertility. They also encounter adverse environments that require adaptive responses. Organisms therefore face selective pressure to mitigate these deleterious effects. During evolution, individual organisms with new genetic variants that reduce or suppress detrimental effects will have selective advantages over those that do not have these modifier effects. With time, complex networks of functional interactions evolve to buffer individuals from both deleterious mutations and environmental perturbations. These networks provide genetic buffering and homeostasis, both of which are the focus of research on the systems biology of health and disease.

Ongoing discussions about the safety of several widely used drugs reflect the fact that developing effective and safe treatments for disease is profoundly difficult. Modifier genes represent a potentially powerful alternative. Their occurrence in healthy persons demonstrates their apparent safety; their ability to mute or suppress disease is evidence of their efficacy. Perhaps, once their mechanisms of action are understood, their benefits can be harnessed to prevent or treat disease. Perhaps the background noise of modifier genes can begin to silence the adverse effects of genes that cause disease.

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