Review

Does your gene need a background check? How genetic background impacts the analysis of mutations, genes, and evolution

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The premise of genetic analysis is that a causal link exists between phenotypic and allelic variation. However, it has long been documented that mutant phenotypes are not a simple result of a single DNA lesion, but are instead due to interactions of the focal allele with other genes and the environment. Although an experimentally rigorous approach focused on individual mutations and isogenic control strains has facilitated amazing progress within genetics and related fields, a glimpse back suggests that a vast complexity has been omitted from our current understanding of allelic effects. Armed with traditional genetic analyses and the foundational knowledge they have provided, we argue that the time and tools are ripe to return to the underexplored aspects of gene function and embrace the context-dependent nature of genetic effects. We assert that a broad understanding of genetic effects and the evolutionary dynamics of alleles requires identifying how mutational outcomes depend upon the 'wild type' genetic background. Furthermore, we discuss how best to exploit genetic background effects to broaden genetic research programs.

What are genetic background effects?

Although many traits vary phenotypically (and genetically) in natural populations, some appear qualitatively similar across unrelated individuals, provided those individuals possess a 'wild type' genotype. This phenomenon is often depicted with 'genotype–phenotype maps', diagrams illustrating how similar phenotypes can be produced despite variation in both genotypes and in underlying intermediate phenotypes such as gene expression (Figure 1a). However, when particular mutations (whether induced or natural variants) are placed into each of these different wild type backgrounds, the phenotypic consequences of that allele may be profoundly different (Figure 1b) [1–3]. Two visibly striking examples of such effects can be found with mutations influencing wing development in *Drosophila* and in sexual characteristics of the tail in *C. elegans* (Figure 2a,b). Despite apparent phenotypic similarity in the wild type state (or in particular environments), there may be considerable segregating genetic variation influencing mutational effects. This so-called 'cryptic genetic variation' has been the subject of several recent studies with respect to its evolutionary potential [4–11]. Simply put, not all 'wild types' are equal.

Genetic background effects have been observed in most genetically tractable organisms where isogenic (or pseudo-isogenic) wild type strains are used, including mice, nematodes, fruit flies, yeast, rice, *Arabidopsis*, and bacteria [12–19]. Such effects have also been observed across the spectrum of mutational classes including hypermorphs, neomorphs, hypomorphs, and amorphs [13,16,20,21]. Because they traditionally have been controlled for as 'nuisance' variation rather than studied as interesting genetic

Glossary

Amorph/hypermorph/hypomorph/neomorph: mutant alleles exhibiting no activity, increased activity or expression, reduced activity or expression, and some novel activity, respectively.
Cryptic genetic variation: genetic variation present in a population that is not phenotypically expressed under benign or ambient conditions, but which may be visible upon genetic or environmental perturbations.
Expression quantitative trait locus (eQTL): a sequence polymorphism in the genome associated with variation in gene expression.
Expressivity: the extent to which a mutant genotype is phenotypically expressed in an organism. Often, mutations may display variable expressivity: in other words, multiple individuals carrying the same mutation may vary for the phenotypes induced by the mutation.
Genetic background: the entire genetic and genomic context of an organism; the complete genotype of an organism across all loci.
Introgression: the introduction of an allele or alleles from one population into another by repeated backcrossing.
Isogenic: having identical (or nearly identical) genotypes.
Line/strain: a distinct interbreeding population, usually maintained in the laboratory, and which is isolated from other such populations, often generated by inbreeding.
Penetrance: the proportion of individuals in a sample with a particular genotype that express the 'expected' phenotype.
Potentiating/permissive mutations: mutations that are required to occur first for subsequent mutations to be expressed.
Wild type: the 'average' phenotype, often assumed to be the 'normal' phenotype, found in natural populations and/or any subpopulation or inbred lines derived from such a population. The genotypes producing such a phenotype are often considered to be wild type genotypes.

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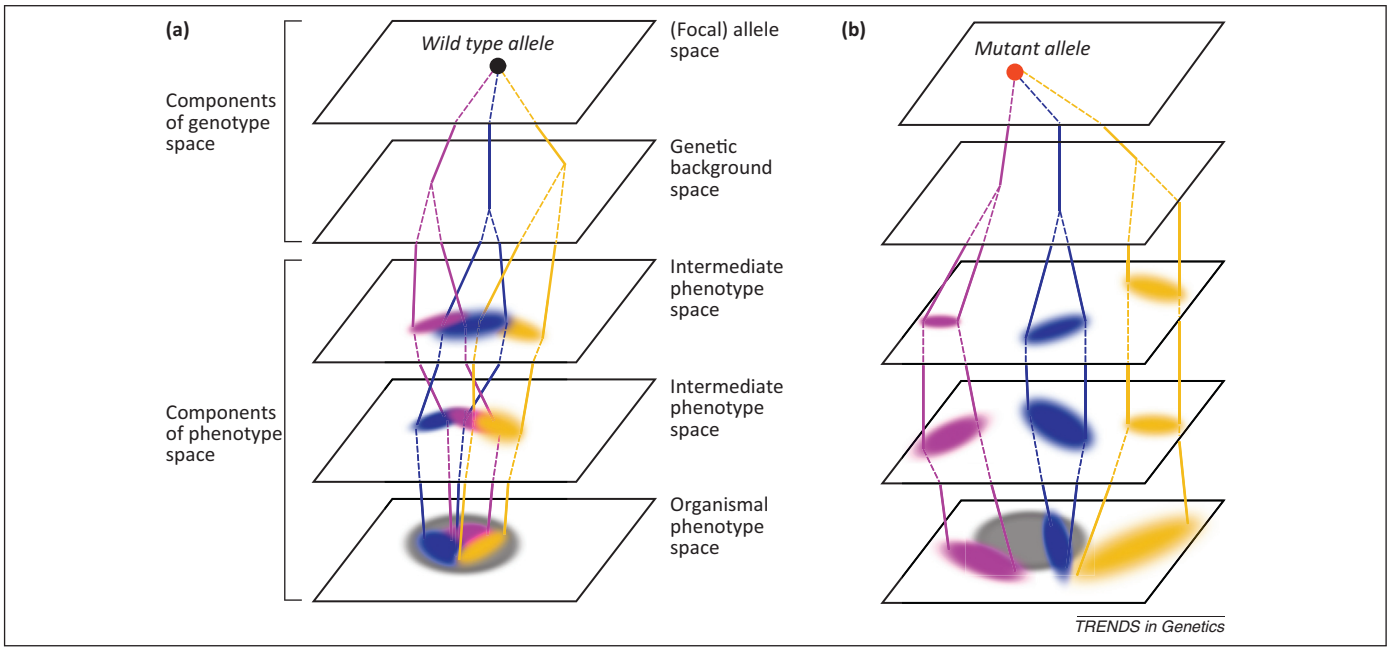

Figure 1. Genetic background effects can be conceptualized in the framework of a genotype–phenotype (G-P) map [72–75]. **(a)** A wild type genotype at a particular locus results in a wild type final phenotype (grey circle), even though there may be variation in intermediate (e.g., gene expression) and 'final' phenotypes among different genetic backgrounds (or in different environments). Each color represents a distinct genotype or strain. **(b)** However, when a particular gene is mutated, intermediate variation among different genetic backgrounds may be expressed in the form of distinct final mutant phenotypes [with some possibly overlapping with the range of wild type phenotypes (grey circle) and others being distinct]. The general increase in variation between backgrounds under the mutational perturbation (i.e., the 'cryptic genetic variation') is depicted by the broader distributions of final phenotypes in panel (b). Finally, although this and many other representations of the G–P map represent the genotypic space as a simple projection (much like the intermediate 'phenotypic' spaces), it is important to remember that the different genotypic spaces interact as well (i.e., the phenotypic outcomes depend on the position in both genotypic spaces, not simply the position in the 'lowest' genotypic space).

phenomena in their own right, background-dependent effects are likely to be even more prevalent than current evidence suggests. Here we discuss the importance of considering genetic background effects not only to increase awareness of this issue but also to argue that by exploiting this variation and integrating knowledge of genetic background, researchers will find increased opportunities for genetic analysis.

Are genetic background effects consequential?

It may be comforting to think that, despite their potential ubiquity, background-dependent effects have only a modest influence on inferences about gene function, but the evidence suggests otherwise. Genetic background effects have been implicated in several recent studies, providing explanations for contradictory outcomes and even overturning long-accepted results. Several key examples (Boxes 1 and 2) illustrate that careful consideration of genetic background is crucial for at least two reasons: (i) failure to control for the genetic background may cause allelic effects at a focal locus to become confounded with variation at other background loci, leading to faulty inferences; and (ii) epistatic interactions between a focal gene and the genetic background

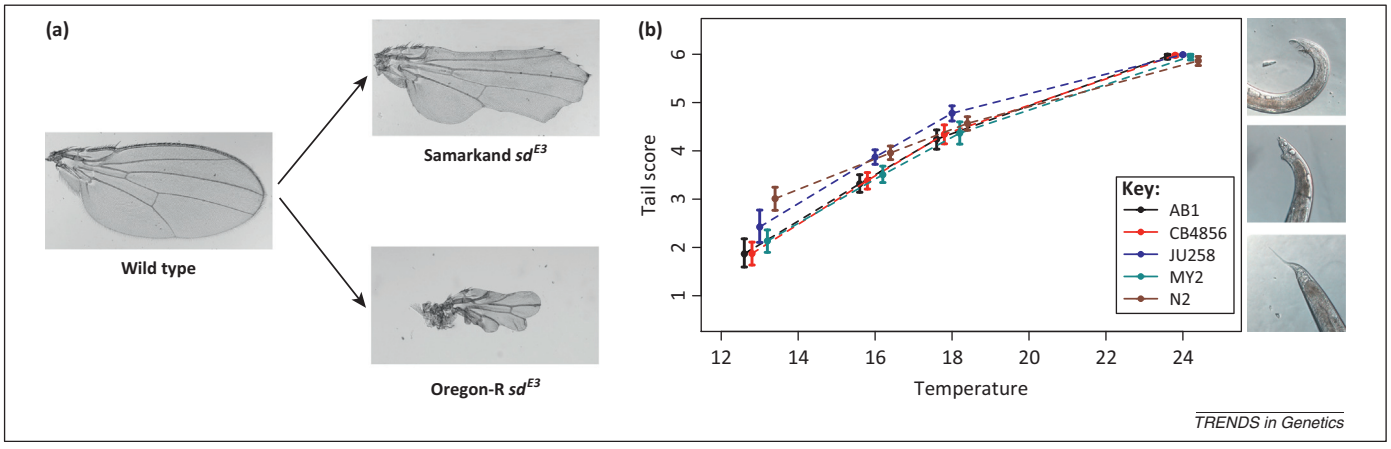

Figure 2. Induced mutations often have qualitatively or quantitatively variable effects on organismal phenotypes in different genetic backgrounds and in different environments. These effects can range from mild (in some cases perhaps even resulting in phenotypes that are indistinguishable from the wild type) to severe. **(a)** The *scalloped*^{E3} allele has qualitatively distinct effects on wing morphology in two commonly used wild type strains of *Drosophila melanogaster*, despite the wild type wings being qualitatively similar across these backgrounds. These background effects extend to include epistatic interactions between *sd* and other loci [1]. **(b)** The effects of the *tra-2*(*ar221*); *xol-1*(*y9*) genotype on sexual differentiation in the tail of *Caenorhabditis elegans* vary quantitatively with both rearing temperature and wild type genetic background [2]. The effects of genetic background are most apparent at intermediate temperatures.