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Genetic backgrounds and hidden trait complexity in natural populations

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Dissecting the genetic basis of natural phenotypic variation is a major goal in biology. We know that most traits are strongly heritable. However, their genetic architecture is a long-standing question, which is unfortunately confounded by the lack of complete knowledge of the genetic components as well as their phenotypic effect in a specific genetic background. Many genetic variants are known to affect phenotypes but the same functional variant can have a different effect on the phenotype in different individuals of the same species. Understanding the impact of genetic background on the expressivity of a given phenotype is essential because this effect complicates our ability to predict phenotype from genotype. Here, we briefly review recent progress on the exploration of the effect of genetic background and we discuss how a deeper characterization of the inheritance, expressivity and genetic interactions hidden behind the phenotypic landscape of natural variation could provide a better understanding of the relationship between genotype and phenotype.

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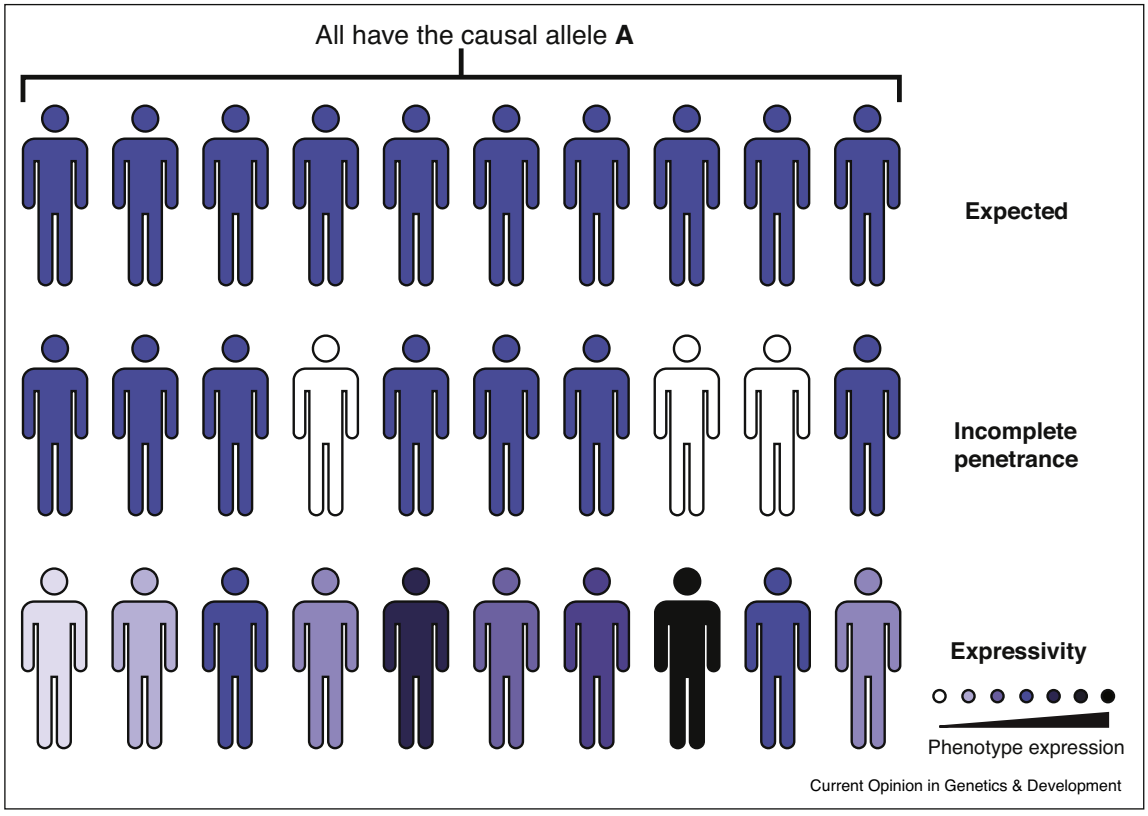
Introduction

Highlighting the rules that govern trait variations in natural populations is a major goal in modern biology. And identifying the underlying genetic causes of such variation is very challenging. Despite the importance of understanding the genetic basis of complex traits, we currently lack complete knowledge of the relevant genetic components, even in scenarios where environment and other non-heritable contributing elements are well controlled [1]. The impact of genetic backgrounds, *inter alia*, on the phenotypic expression are still poorly understood to date. However, we argue here that a better understanding of background-specific effect on phenotypic expression variation would lead to a greater perception of the genotype–phenotype relationship.

Monogenic mutation, penetrance and expressivity

More than 150 years after Gregor Mendel laid the basis of genetics with his laws of heredity and experiments on hybrids [2], we still lack a general understanding of the genetic architecture of traits. For the past century, Mendelian and complex traits have been considered at the opposite ends of the phenotypic spectrum. The inheritance patterns of traits are usually classified as either monogenic, strongly influenced by variation within a single gene, or complex, resulting from variation within multiple genes and their interaction. While useful, this dichotomy is an overly simplistic and artificial view in most of the cases observed in natural populations. Almost from the beginning of modern genetics, the relevance of the genetic context or background was recognized when William Bateson coined the term epistasis to describe the departures from expected Mendelian ratios in his experimental crosses [3]. Behind the simplicity of a Mendelian inheritance, there is a clear hidden complexity of how variants exert a functional impact among individuals of the same species. Although this has been known for decades, the continuous level of the underlying phenotypic spectrum is overlooked. It is evident that most monogenic mutations do not always strictly follow Mendelian inheritance [4]. Many genetic disorders are referred as Mendelian that is caused by monogenic mutations. However, people inheriting the same mutation often display variation in phenotypic expression. This has come to be described by two words: 'penetrance' and 'expressivity' [5,6]. First, a mutation can exhibit incomplete penetrance, meaning that an individual may have this particular mutation but may not express the expected phenotype because of modifiers, epistatic interactions or suppressors present in the genome or because of the environment (Figure 1a). An example is the *BRCA1* alleles, which predispose to breast and ovarian cancer in humans. Individuals with a mutation in the *BRCA1* gene have a ~80% risk to develop this disease, therefore showing incomplete penetrance [7]. Second, the penetrance of a mutation is sometimes 100%, meaning that all the individuals present the expected trait (Figure 2a), but they exhibit different degrees of expressivity. Neurofibromatosis type I, a Mendelian disorder, is a notorious example of large variable expressivity. The disease is caused by dominant mutations in the *NF1* gene [8] and

Figure 1



Penetrance and expressivity of traits. In the case of a monogenic disease, all individual carrying the causal allele are expected to develop the same trait. However, in some cases, individuals with the causal allele do not express the expected phenotype, resulting in incomplete penetrance. For other traits, the phenotype will be expressed differentially in different individuals: some will develop more severe symptoms while others display milder symptoms thus representing phenotypic expressivity.

individuals carrying a mutation show a significant phenotypic heterogeneity. In fact, this is the case of a large number of diseases referred as caused by mutations occurring in single genes such as cystic fibrosis, Huntington's disease, and Fragile X [9–11]. In the case of cystic fibrosis, there is even evidence that modifiers, that is mutations in other genes, impact the phenotype [12,13]. Even for Down Syndrome, a whole chromosome disorder, there is evidence of phenotypic expression variation due to genetic background differences [14,15]. More broadly, the phenotypic expression can be modified by various factors with the two most reported being age [7] and sex [16]. However, phenotypic expression can also be impacted by genetic background with the presence of genetic interactions and modifiers as already mentioned, mutation type [17] and environment [18].

The distinction between penetrance and expressivity reflects an overly simplified view for several reasons. First, the full breadth of expression is not systematically characterized for any monogenic mutation in humans. Second, considerable uncertainty is introduced at the phenotypic level, because it is difficult to accurately characterize a trait measurement for most genetic disorders. Most diseases are obviously a complex layering of intermediate molecular traits, for example gene expression, methylation, protein and metabolite levels. Several layers of intermediate molecular traits account for the global phenotype at the individual level. Thus, two individuals can display the same trait at the organism level but exhibit completely different intermediate phenotypes at the molecular level, or vice versa (Figure 2). To better understand the genetic basis of diseases, a more precise estimation of the phenotypic value as well as a more complete picture of the genetic architecture of the molecular traits are probably essential.

Genetic backgrounds, natural populations and model organisms

Variation among individuals of natural populations provides useful raw material to dissect the relationship between genetic variants and phenotypes [19–22]. Moreover, high-throughput genotyping and phenotyping technologies have greatly enhanced the power to dissect the genetic complexity hidden behind traits in model as well as in non-model organisms [23]. A focus on the effects of