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Genetic architecture of quantitative traits and complex diseases

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More than 150 years after Mendel discovered the laws of heredity, the genetic architecture of phenotypic variation remains elusive. Here, we discuss recent progress in deciphering how genotypes map onto phenotypes, sources of genetic complexity, and how model organisms are illuminating general principles about the relationship between genetic and phenotypic variation. Moreover, we highlight insights gleaned from large-scale sequencing studies in humans, and how this knowledge informs outstanding questions about the genetic architecture of quantitative traits and complex diseases. Finally, we articulate how the confluence of technologies enabling whole-genome sequencing, comprehensive phenotyping, and high-throughput functional assays of polymorphisms will facilitate a more principled and mechanistic understanding of the genetic architecture of phenotypic variation.

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Introduction

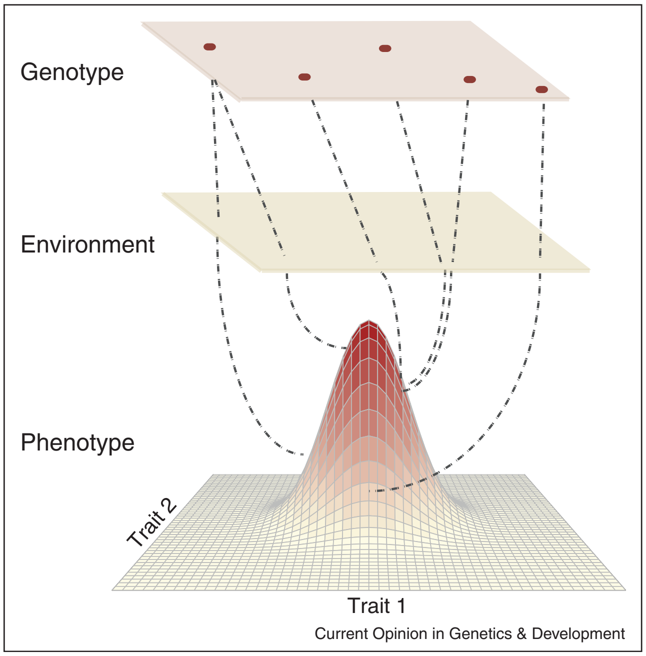
One of the most ubiquitous characteristics of life is the incredible phenotypic diversity that exists within and between species. Delineating the heritable basis of phenotypic variation remains a fundamental goal of applied, basic, and biomedical research [1]. Although our understanding of how genetic diversity maps onto phenotypic diversity is becoming increasingly sophisticated, formidable gaps in knowledge remain. Of particular interest, and complexity, is elucidating the genetic architecture of quantitative traits and complex diseases. To be clear, the genetic architecture of a trait refers to a comprehensive description of how genes and the environment conspire to produce phenotypes (Figure 1), including the number of quantitative trait loci (QTL) that contribute to variability of the trait between individuals, their effect sizes, whether alleles for causal polymorphisms are additive, dominant, or recessive and their frequency in the population, patterns of gene–gene and gene–environment effects, and levels of pleiotropy [2]. There is an extensive literature on the genetic architecture of quantitative traits, and many excellent recent reviews exist [2–5]. Here, we specifically focus on recent discoveries that illuminate general principles of genetic complexity and its implications for understanding the genetic architecture of quantitative traits and complex diseases. Although we focus primarily on humans, important insights into the genetic architecture of phenotypic diversity gleaned from model organisms will also be discussed.

Architectural diversity across traits

There is enormous architectural diversity, or genetic complexity, across traits. For example, human diseases span the range of ''simple'' Mendelian traits, such as Cystic Fibrosis that result from mutations of large effect size in the *CFTR* gene [6], to exceedingly complex traits such as height that are likely influenced by thousands of variants and environmental factors [7]. Note, even simple Mendelian traits can exhibit striking levels of allelic and locus heterogeneity [8]. For instance, nearly 2000 mutations have been identified in the *CFTR* gene that lead to Cystic Fibrosis [9], and variation at additional loci can modulate the severity of symptoms [10].

Furthermore, considerable architectural diversity is also observed even among closely related phenotypes. For example, numerous studies have been performed to elucidate the genetics of gene expression, where transcript abundance is treated as a quantitative trait and expression QTL (eQTLs) are mapped by linkage or association methods [11,12]. A powerful feature of this study design is that thousands of phenotypes are studied, allowing insights into the distribution of architectures across traits. The first eQTL study was performed in the budding yeast *Saccharomyces cerevisiae* [13••] by crossing two divergent parental strains (BY and RM) and mapping eQTLs among the progeny. The median heritability of gene expression traits was 84% [13••]. The majority of eQTLs detected, however, had modest effects and explained a median variance of 27%. Subsequent modeling showed that only 3% of highly heritable transcripts are consistent with single-locus inheritance, 17–18% are consistent with control by one or two loci, 50% of all transcripts have at least five additive QTLs, and 20% have at least 10 additive QTLs [14]. Thus, even in a simple eukaryotic organism grown in a controlled environment, the genetic architecture of gene expression levels encompasses a range of complexity.

Figure 1



Schematic illustration of the mapping of genotypes onto phenotypes. The top two rectangles represent the set of all possible genotypic and environmental states, respectively. Genetic architecture refers to the rules that govern how a set of multilocus genotypes maps onto phenotypes, and how the environment influences this mapping. Genotype space can be extremely large with 3^n possible multilocus genotypes, where n denotes the number of trait influencing variants. Lines represent the mapping of particular multilocus genotypes (red circles) in particular environments to trait values. For simplicity, phenotypic space is only shown for two traits (the height of the bivariate distribution indicates population frequency). *Note*: identical genotypes in different environments can culminate in different phenotypic values (representing gene–environment interactions) and distinct genotypes either in the same or different environments can result in the same phenotypic values (representing robustness).

Finally, it is important to note that formally defining a measure of architectural diversity that quantifies genetic complexity remains challenging. The number of loci that govern variability of a trait is often used as an implicit measure of genetic complexity. However, this is a rather crude summary that fails to account for potentially important architectural features such as gene–gene and gene–environment interactions. Recently, Thompson and Galitsky [15] proposed a more formal measure of genetic complexity, which they defined as the excess of genotypic diversity over phenotypic diversity, and used this framework to investigate the level and determinants of genetic complexity in Boolean networks. Interestingly, higher levels of genetic complexity were associated with topological features of the network and the number of periodic attractors (such as observed in cell cycle networks) [15]. Although this is an important step towards more rigorously defining and quantifying genetic complexity, additional theoretical work in this area is needed.

GWAs—so many associations, so little variation explained

With the advent of high-density SNP arrays, genome-wide association studies (GWAs) have been performed at a frenetic rate in humans. Indeed, a catalog of published GWAs [16] (http://www.genome.gov/gwastudies/) includes 1659 publications and 10,986 associated SNPs as of July 24, 2013. As expected from this study design, most of the reported disease/trait associated SNPs are common with small effect sizes (i.e., odds ratio <1.5). Notably, the considerable number of significant associations fails to account for a substantial fraction of heritability for most traits studied to date, an observation that has been dubbed the ''missing heritability'' problem [5,17]. For example, 54 validated variants have been associated with human height, a classic complex trait with an estimated narrow sense heritability (the proportion of phenotypic variance that is due to additive genetic variance) of 80%; yet these 54 QTLs account for only ~5% of the variation in height observed among the tens of thousands of individuals studied [18]. Similarly, in a study of more than ten thousand individuals to identify loci that contribute to the risk of Crohn's disease, the 32 identified loci explain ~20% of disease heritability [19]. Note, an association that explains only a small proportion of heritability may nonetheless provide valuable biological insights that could prove useful in designing drug targets [17,20]. However, the missing heritability revealed in many well-powered GWAs clearly highlights that many important architectural details of traits remain to be discovered. Below, we discuss features of genetic architecture that likely contribute to why GWAs fail to account for substantial amounts of heritability.

Detecting the undetectable—many loci of small effect

The infinitesimal model, proposed by Fisher nearly a century ago [21], has been a key conceptual foundation in the analysis of quantitative traits [22]. It posits that quantitative trait variation (or disease liability) is dictated by a large number of loci that have very small effect sizes. Thus, one potential explanation for why GWAs with even tens of thousands of individuals fail to reveal substantial amounts of heritability is simply because of inadequate statistical power. Consistent with this hypothesis, Yang *et al.* [23] examined variation in height in an Australian population and found that 294,000 SNPs examined could collectively explain 45% of the phenotypic variance, the vast majority of which fail to meet stringent significance thresholds because of their small effect sizes. Obviously, larger sample sizes can increase the statistical power to detect variants with weak effects, but there are practical limitations to detection, particularly for rare variants.

Model organism studies also clearly demonstrate that the architecture of some traits is governed by many loci of small effect. Specifically, a recent study in yeast measured growth rates in different environments and found that the

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