Review

Cell PRESS

The genomic determinants of genotype × environment interactions in gene expression

Vladislav Grishkevich and Itai Yanai

Department of Biology, Technion – Israel Institute of Technology, Haifa 32000, Israel

Predicting phenotype from genotype is greatly complicated by the polygenic nature of most traits and by the complex interactions between phenotype and the environment. Here, we review recent whole-genome approaches to understand the underlying principles, mechanisms, and evolutionary impacts of genotype × environment (G×E) interactions, defined as genotype-specific phenotypic responses to different environments. There is accumulating evidence that G×E interactions are ubiquitous, accounting perhaps for the greater part of the phenotypic variation seen across genotypes. Such interactions appear to be the consequence of changes to upstream regulators as opposed to local changes to promoters. Moreover, genes are not equally likely to exhibit G×E interactions; promoter architecture, expression level, regulatory complexity, and essentiality correlate with the differential regulation of a gene by the environment. One implication of this correlation is that expression variation across genotypes alone could be used as a proxy for G×E interactions in those experimental cases where identifying environmental variation is costly or impossible.

From single traits to a whole-genome perspective

Although the genotype of an individual is now straightforward to determine, our inability to predict its phenotype has never been more self-evident. Tremendous progress has been made resolving certain well-studied traits at the molecular level [1–13]; however, an understanding of the specification of complex traits is generally lacking [14]. Much of this complexity results from the phenotype being a convolution of the genotype and the specific environment experienced by the organism. In this review, we discuss the occurrence of G×E interactions. Here, we first describe the classical and latest methods for identifying these in the population, before turning to emerging principles regarding their appearance. We next discuss the mechanisms that create G×E interactions within the framework of local and distant genetic changes. Finally, we examine the implications of G×E interactions for the development and evolution of species, and provide an outlook for future research on this topic.

When a single trait is examined between two genotypes and two environments, the trait might be constant across all combinations or it might be affected in several possible ways (Figure 1). First, the manifestation of the trait could differ between the genotypes but be unaffected by the environmental changes (Figure 1D). Second, the expression of the trait may be affected by a particular environment, but identically so across the genotypes (Figure 1E). Third, the appearance of the trait might change across both genotypes and environments, but the nature of this change might be additive (genotypic and environmental variation, Figure 1F). Finally, often the environment affects the phenotype in a complicated manner that is not an additive effect of the genotype. Such a genotype-specific phenotypic response to different environments is called a G×E interaction. A G×E interaction may manifest, for example, from a genotypic change between the strains underlying a change in phenotype in only one of the environments (Figure 1A). Alternatively, an environment may have opposing effects across genotypes (Figure 1B). Beyond discrete environments, G×E interactions may also be examined as a function of continuous environments [15–17]. These kinds of G×E interaction represent a considerable challenge for cracking the genotypic code that produces them.

Traditionally, studies of G×E interactions have focused upon individual phenotypic traits, which often include life-history traits, such as body size and longevity [2,4–6,18–24]. To map the genetic loci responsible for the particular G×E interaction, multiple loci in the genome are typically screened. Such quantitative trait locus (QTL) analyses are based on the comparison of the appearance of a trait across recombinant inbred lines (RIL) derived from a cross of two parental strains differing in that trait (Figure 2A) [18,25]. This approach was recently successfully used to explore the effect of low temperature on the body size of the nematode *Caenorhabditis elegans* [2]. The laboratory strain was 33% bigger at lower temperatures; however, in a second strain, body size was unaffected (such as the scenario indicated in Figure 1A). Using QTL analysis, the researchers found that a specific single nucleotide polymorphism (SNP) in *tra-3*, which encodes a calpain-like protease, accounted for the differential response. This QTL approach to identify the genetic basis of G×E interactions has been remarkably fruitful for many traits [2,5,18,20,22–24].

Corresponding author: Yanai, I. (yanai@technion.ac.il).

Keywords: gene regulation; phenotypic plasticity; genetic assimilation; G×E interactions; evolution of gene expression.

0168-9525/$ – see front matter

 http://dx.doi.org/10.1016/j.tig.2013.05.006

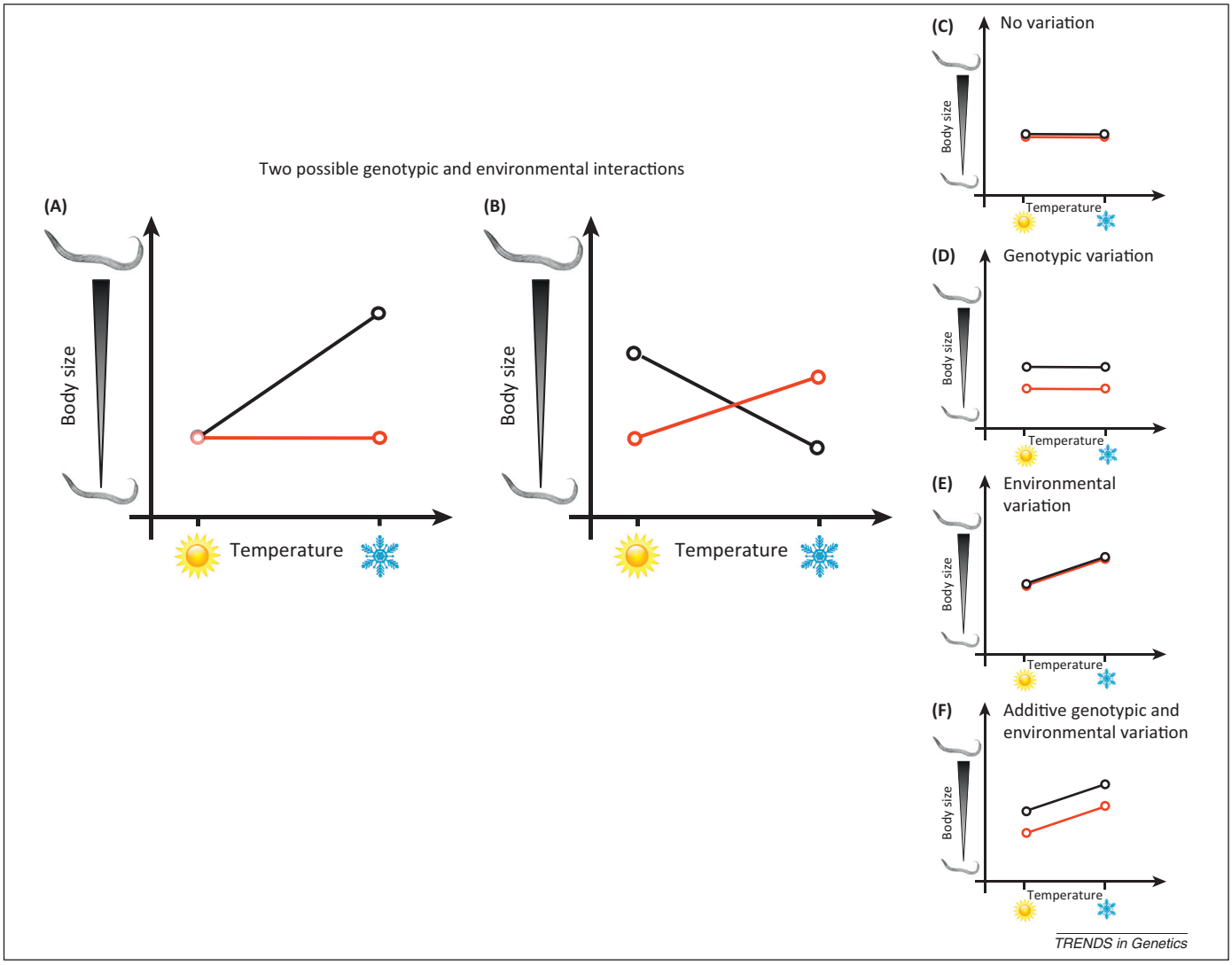

Figure 1. Modes of phenotypic variation across genotypes and environments. A phenotype can vary depending on the genotype or environment, and often a complex interaction between the two leads to unexpected changes in phenotype. **(A,B)** Examples of genotype × environment (G×E) interactions. Two genotypes (strains), indicated by black and red lines and circles, demonstrate different phenotypic outcomes (body size) when exposed to different environments (temperatures). Instances are shown of **(C)** no variation, **(D)** only genotypic variation, **(E)** only environmental variation, and **(F)** both genotypic and environmental variation, although without an interaction.

G×E interactions are extremely common [26] and are observed even when examining a single trait. In an early study examining bristle numbers in *Drosophila* across a set of RILs and environments (temperature and sexual environment), 14 out of the 92 examined markers showed significant G×E interactions, a remarkably high level [23]. More recently, a study queried for G×E interactions in the risk for breast cancer between 23 alleles and ten environmental factors. Examining data from over 70 000 individuals, significant G×E interactions were detected for breast cancer rates for a lymphocyte-specific protein 1 (LSP1) allele and the number of births, and a caspase 8 (CASP8) allele and alcohol consumption [27].

High-throughput techniques have greatly expanded the depth in which traits can be analyzed in terms of the effects of the genotype and the environment, and now promise to reveal generalized principles. For example, using RNA-Seq, tens of thousands of traits in the form of gene expression levels can be simultaneously examined. The first study of global gene expression measurements coupled with linkage analysis demonstrated the power of such an approach, called eQTL analysis (Figure 2A), in unmasking the overall complexity of gene expression variation [25], leading to a shift in the research of gene expression evolution and regulation [28]. This study determined the linkage between expression levels of 6215 genes and 3312 genomic markers in two parental yeast strains and 40 RILs. The analysis revealed that variation in gene expression was associated with *cis*-effects, although a small number of *trans*-effects impacted multiple genes. Later analyses also included different environments in the approach and identified G×E interactions [29]. A shortcoming of this method, however, is the reliance upon RILs, which are labor intensive to construct. Moreover, mapping in the QTL approach can be of limited resolution depending upon the markers used.

A modified approach has been recently introduced to map the effects of G×E interactions on gene expression [30]. Gene expression was monitored across a population of individuals and conditions (environments), followed by whole-genome sequencing to identify each genotype (Figure 2B). This method is akin to genome-wide association studies (GWAS),