Review

MOLECULAR METABOLISM

# Epigenetic control of variation and stochasticity in metabolic disease

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## ABSTRACT

**Background:** The alarming rise of obesity and its associated comorbidities represents a medical burden and a major global health and economic issue. Understanding etiological mechanisms and the causes underpinning susceptibility and therapeutic response is of primary importance. Obesity, diabetes, and metabolic diseases are complex trait disorders with only partial genetic heritability, indicating important roles for environmental programing and epigenetic effects.

**Scope of the review:** We will highlight some of the reasons for the scarce predictability of metabolic diseases. We will provide some evidences about how genetic variants generate phenotypic variation in disease susceptibility across populations. We will then focus on recent conclusions about epigenetic mechanism playing a fundamental role in increasing variability.

**Major conclusions:** Predicting the phenotypic outcome considering all the implicated variables is not easy. We are at the beginning of a long quest for fundamental players dictating phenotypic variation between individuals. Dissecting what are the molecular mechanisms governing these phenomena will be a discovery of paramount importance. It will impact basic biology, providing us with a better understanding of how cells work, of evolutionary processes as well as of the "missing heritability" issue, thus having a huge influence on our ability to move towards a truly personalized and precision medicine.



**Keywords** Phenotypic variation; Inheritance; Metabolic diseases; Epigenetics

## 1. INTRODUCTION — PHENOTYPIC VARIATION

Understanding how phenotypic variation arises and the extent to which it is reproducibly plastic are fundamental biological questions. To understand phenotypic variation is to understand mechanisms that shape phenotype and that drive differential disease susceptibility. Variation is the template for natural selection and therefore its investigation is also a means towards understanding speciation. Indirectly, this question has become *the* overarching goal of life science research over the last decades [1].

Simply put, an organism's complex trait composition is the product of genetic, epigenetic, and environmental inputs and their cumulative interactions through development (Figure 1). The genetic mechanisms that control complex traits are 'Mendelian' in their transmission pattern (with some exceptions) and comprise DNA-sequence differences. Epigenetic contributors, by contrast, are 'non-Mendelian' and rely on mechanisms that bypass DNA sequence to impart phenotype. Non-Mendelian or epigenetically-driven phenotypic variation (EPV) can be thought of, anecdotally, as variability that occurs in inbred populations, and can be classified according to distribution as either continuous (e.g. height) or discrete (e.g. flower color), or a combination (eusocial insect morphs). The latter examples are termed 'polyphenisms', scenarios in which the same genotype yields distinct phenotypes within a population, with no intermediates (e.g. worker and soldier ant). To the best of our knowledge, both continuous EPV and polyphenisms result predominantly from developmental responses to the environment (Figure 2), a broader phenomenon termed 'phenotypic plasticity'.

Studies suggest that phenotypic plasticity is triggered preferentially during critical windows of high sensitivity including embryonic development and growth phases (Figure 3). More recently, the preconceptual germlines of the parents, and even ancestral germlines, have been highlighted as 'intergenerational' windows of sensitivity for triggering plasticity (Figure 4).

## 2. MENDELIAN PHENOTYPIC VARIATION — THE TEMPLATE FOR PLASTICITY

While single genetic variants alone are of course capable of causing disease (e.g. 'MODY' diabetes mutations), complex traits such as glycemia represent the physiological output of many contributing genetic loci and are therefore typically normal or log-normal distributed. Experimentally, mapping genetic architectures that drive complex traits is challenging. Quantitative physiological traits typically represent the integrated output of numerous cellular, tissue-specific, and inter-tissue effects. Blood glucose for example integrates organismal behaviors [exercise, depression etc.], multiple tissue responses [liver, muscle, adipose, etc.], and different hormonal axes [cortisol, glucagon, insulin, etc.], all of which comprise many gene interaction networks that are dynamic again to the environment. Most

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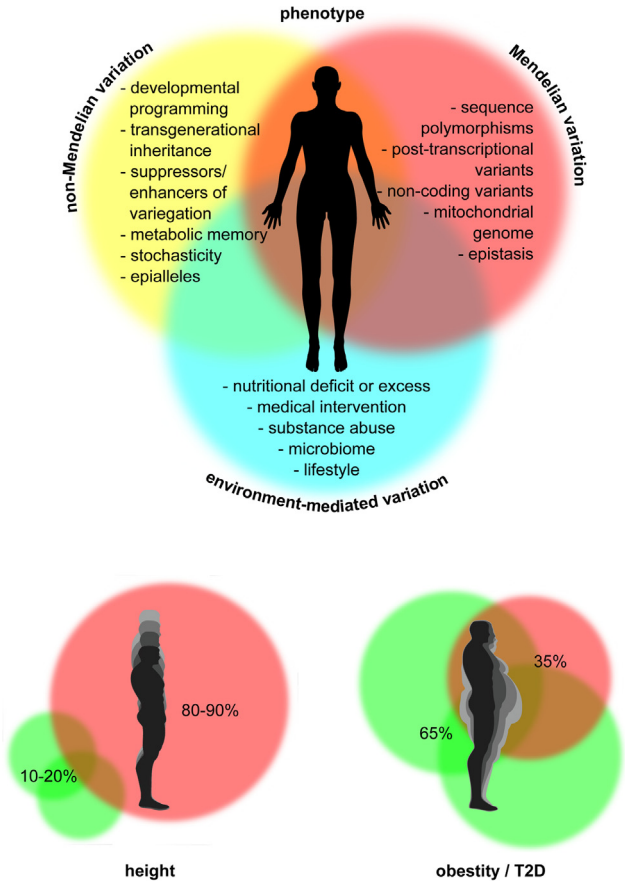


**Figure 1: Modes of variation impacting on phenotype**. Mendelian variation, non-Mendelian variation and the environment concur to modify the phenotypic outcome of an individual, often intermingling into each-other. The contribution of Mendelian variation to height determination is estimated around 80–90%, whereas for obesity/ T2D estimates are lower (~35% heritability).

disease traits, in turn, are composites of *many* complex traits, exacerbating the challenge. Further, at the genic level, dozens, if not hundreds, of relevant alleles can exist in the population. A recent survey of coding sequence variation across 60,706 individuals identified 7.9% of high-confidence regions as multiallelic, i.e. contained multiple distinct sequence variants [2]. LDLR, the gene coding for the receptor for low-density lipoprotein (LDL) cholesterol [3], contained over 500 different missense mutations and 200 small insertions and deletions across the population. The challenges and complexities of quantitative trait genetics in the human population can be found here [4].

So, while DNA-sequence differences are the major contributors to population-level variation and they are not trivial to map, they represent the template upon which epigenetic mechanisms can act. Briefly therefore, sequence variations themselves include:

### 2.1. A range of variant types

Phenotypic variation can result both from gain- and loss-of-function mutations. Both can arise from DNA sequence insertions, deletions, and copy number variations (CNVs), simple mechanisms that affect gene dosage. Large deletions and duplications have been reported in many genes related to metabolic syndrome, including the *LDLR*, the lipoprotein lipase (*LPL*) and lamin B (*LMNB2*) genes [5].

### 2.2. Variants in non-protein-coding genes

The ~98.5% of our genome is non-protein-coding: it is pervasively transcribed, and its transcripts can support regulatory function [6,7]. Among the best functionally characterized non-coding RNAs (ncRNAs) arising from these sequences are microRNAs (miRNAs). These transcripts have been shown to be involved in conferring to cells [8] as well as in invertebrates and insects [9] biological robustness [10]: the ability of maintaining the phenotype in spite of internal or external perturbations [11]. Interestingly, lncRNAs have been recently shown to exhibit higher natural expression variability among individuals compared to protein-coding genes [12].

### 2.3. Epistasis and background effects

Because of the extreme interconnectivity of cell regulatory networks, even at the cellular level, predicting the impact of a sequence variant is difficult as the variation acts in the context of all other variants and their potential additive, synergistic and antagonistic interactions. This phenomenon is known as epistasis [13]. Recently, mouse chromosome substitution strains (CSSs) were used as a model to map quantitative trait loci (QTLs) on a fixed genetic background. Analysis of CSSs indicate that epistatic interactions control the majority of the heritable variation in both fasting plasma glucose levels and hepatic

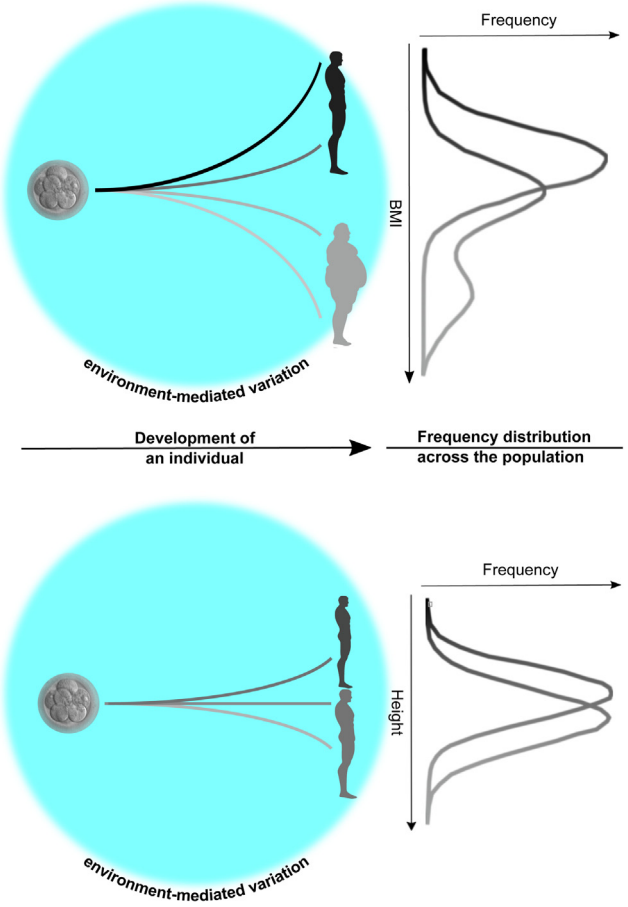


**Figure 2: Distributions of phenotypic variation.** Non-Mendelian phenotypic variation acts during development and can be described either as a discrete, combined or as a continuous distribution. In the first scenario the traits subject to the variation are termed 'polyphenic' (here exemplified by BMI, whereas height is exemplifying continuously varying traits).

 