Cell Metabolism
Perspective

A Next Generation Multiscale View of Inborn Errors of Metabolism

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Inborn errors of metabolism (IEM) are not unlike common diseases. They often present as a spectrum of disease phenotypes that correlates poorly with the severity of the disease-causing mutations. This greatly impacts patient care and reveals fundamental gaps in our knowledge of disease modifying biology. Systems biology approaches that integrate multi-omics data into molecular networks have significantly improved our understanding of complex diseases. Similar approaches to study IEM are rare despite their complex nature. We highlight that existing common disease-derived datasets and networks can be repurposed to generate novel mechanistic insight in IEM and potentially identify candidate modifiers. While understanding disease pathophysiology will advance the IEM field, the ultimate goal should be to understand per individual how their phenotype emerges given their primary mutation on the background of their whole genome, not unlike personalized medicine. We foresee that panomics and network strategies combined with recent experimental innovations will facilitate this.

Introduction

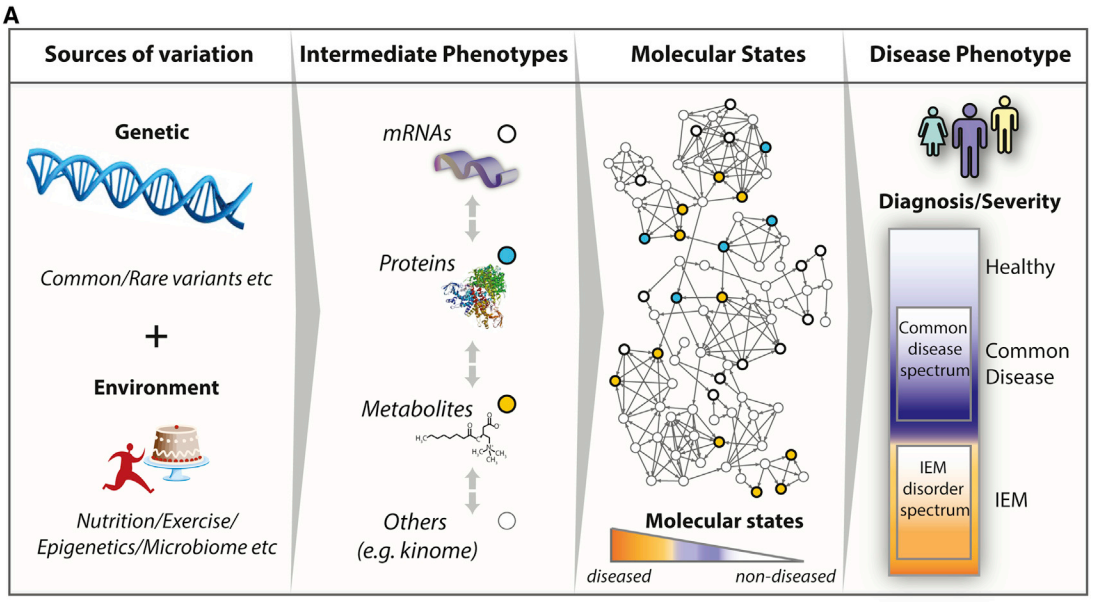
The term "inborn errors of metabolism" (IEM) was first coined in 1902 by Archibald Garrod, who is attributed to being the first to connect a human disorder with Mendel's laws of inheritance (Garrod, 1996). It describes a class of inherited genetic diseases caused by mutations in genes coding for proteins that function in metabolism. The disease may be the result of the accumulation of toxic substrates or essential products being intolerably low. Although IEM occur in every biochemical pathway, historically they have been grouped in specific classes such as amino acidemias, organic acidurias, and lysosomal storage disorders. An example of the latter is Gaucher disease (GD), which is caused by deficient activity of the lysosomal enzyme beta-glucocerebrosidase due to mutations in the encoding gene (*GBA*). As a consequence, the substrate of GBA, glucosylceramide, accumulates in the lysosome, especially of tissue macrophages of the liver, bone marrow, and spleen, thereby causing damage in hematological, skeletal, and nervous systems (Baris et al., 2014). The incidence of IEM varies greatly and depends on the population. Some of the more frequent IEM are phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency with respective incidences of 1 in 10,000 and 1 in 20,000 (Schulze et al., 2003; Wilcken et al., 2003). Most other IEM are much rarer with sometimes only a few or even one unique case diagnosed. Treatment has improved but often remains insufficient (Vernon, 2015).

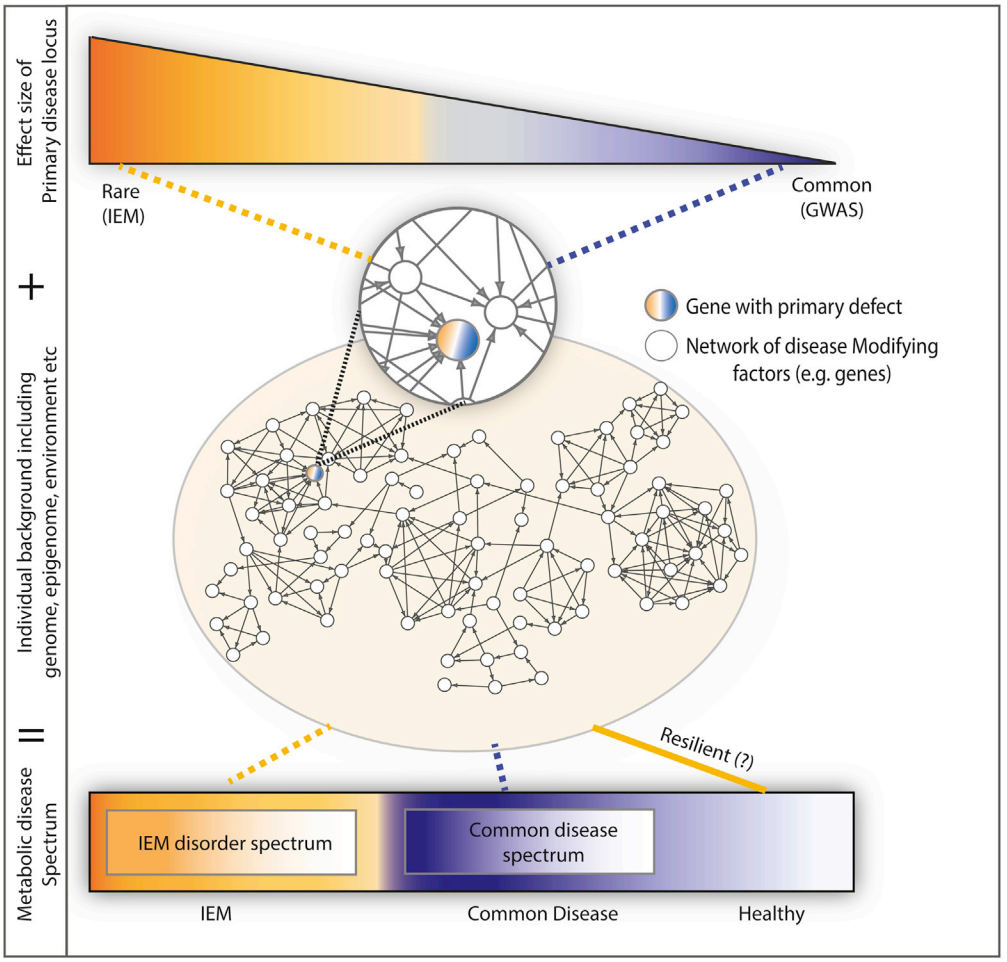
IEM Are Not Unlike Complex Disease

In a bird's eye view, IEM are Mendelian traits caused by single-gene mutations, which has led to the one gene-one disease paradigm. Garrod alluded to this by concluding that an individual with alkaptonuria would either have the disease or not and that there were essentially no shades of gray (Garrod, 1996). However, time has shown that IEM are also not unlike common diseases for the major reason they often present as a spectrum of disease phenotypes in which a clear correlation between the severity of mutation at the affected locus and the phenotype (genotype-phenotype correlation) is lacking (Dipple and McCabe, 2000a, 2000b; Lanpher et al., 2006; Scriver and Waters, 1999).

The classic autosomal recessive disease PKU illustrates this oversimplification. Initially, mutations at the human phenylalanine hydroxylase locus (*PAH*) were deemed sufficient to explain the impaired function of the enzyme PAH, the associated metabolic phenotype, elevated plasma phenylalanine levels, and the resultant clinical phenotype, mental retardation (Scriver and Waters, 1999). However, PKU was subsequently found to arise from different genetic defects (e.g., tetrahydrobiopterin homeostasis) and be influenced greatly by diet (e.g., protein intake), and importantly, the PAH genotype and predicted effect on enzymatic function often failed to consistently predict the extent of cognitive and metabolic phenotypes in the PKU patient. Importantly, PKU was not an exception to the rule, as this oversimplification of one gene-one disease paradigm was also challenged in many other monogenic diseases. In summary, the prevailing view of the last two decades is that monogenic traits do conform to long-accepted ideas about the expression of major loci and their importance in determining parameters of phenotypes; however, the associated features (such as cognitive behavior in PKU) are complex in nature and not unlike those in so-called complex traits (Scriver and Waters, 1999).

It has been over 15 years since IEM have been viewed as complex traits (Dipple and McCabe, 2000a, 2000b; Scriver and Waters, 1999). It is therefore surprising that despite avid application of unbiased systems biology and omics approaches to unravel complex diseases (Ritchie et al., 2015) there are few examples of their use in the IEM field. It appears as if complex methodologies are deemed not needed or not applicable. This





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