PERSPECTIVES: GENETICS

The Land Between Mendelian and Multifactorial Inheritance

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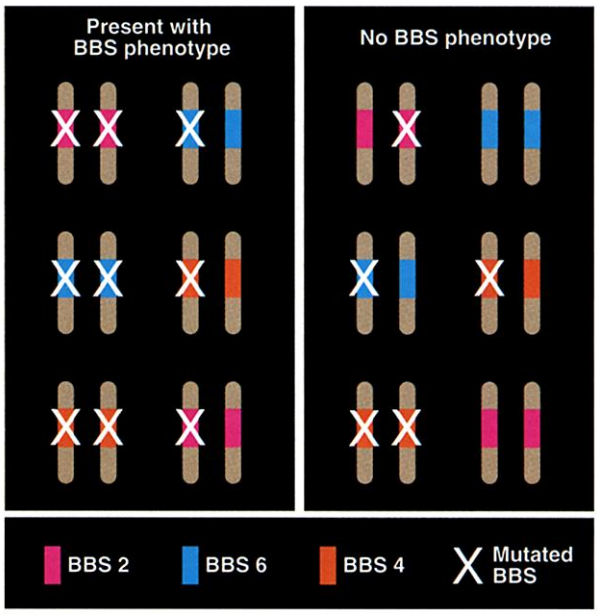
Genetic disorders are often divided into Mendelian and multifactorial traits. In classical Mendelian inheritance, a change in observable features (phenotype) arises as a consequence of mutations in one (dominant) or both (recessive) copies of a gene. In contrast, multifactorial diseases such as diabetes, asthma, and heart disease are caused by mutations in more than one gene with a contribution from environmental factors. There has been spectacular success in identifying the genes responsible for Mendelian disorders, whereas finding the susceptibility genes involved in multifactorial diseases has been a struggle (*1*). Indeed, the identification this year of *NOD2* as a susceptibility gene for Crohn's disease has been proclaimed a milestone, leading to the prediction that the floodgates for finding susceptibility genes for other multifactorial disorders will be thrown open (*1*). But how do multiple genes interact to give the final phenotype of a multifactorial disease, and what might we expect?

Understanding the genetic factors underlying common disorders is a difficult but critical task because each gene and environmental factor can contribute a small risk, such as the 15% risk contributed by the *NOD2* gene to Crohn's disease (*2*, *3*). In this regard, there exists a land between simple Mendelian and multifactorial disorders that needs to be charted. This land is inhabited by genes, such as modifier genes and redundant genes, that have many effects on the phenotype. Understanding the mode of action of these genes will help in determining how susceptibility genes may interact to give rise to a multifactorial phenotype. On page 2256 of this issue, Katsanis *et al.* (*4*) report that mutations in two genes rather than one cause Bardet-Biedl syndrome (BBS). The authors term this phenomenon triallelic inheritance because one of the six BBS loci has both copies of the gene mutated (allelic mutation) and the other, which can be any of the remaining five loci, has one copy mutated (see the figure). We submit that this might just as well be termed "recessive inheritance with a modifier of penetrance."



One mutation too many. Complex inheritance in Bardet-Biedl syndrome. Two allelic mutations in one BBS gene and a third mutation in another BBS gene are required for the disease phenotype to become manifest. The question is, what molecular interactions underlie the formation of the BBS phenotype? Three of the six BBS genes have been identified: BBS2 encodes a protein of unknown function, BBS6 is a putative chaperone, and BBS4 may be a glucosamine transferase. Three more BBS loci have been defined by linkage, although the genes have yet to be identified.

BBS is an autosomal recessive condition in which patients present with a heterogeneous phenotype. The primary features of the disease are obesity, polydactyly, pigmentary retinopathy, hypogonadism, renal abnormalities, and mental retardation. Patients can also have diabetes and hypertension, and there is overlap with other syndromes such as McKusick-Kaufman syndrome (*5*). Two questions then arise: What is the correlation between the genetic mutation (genotype) and phenotype for the six BBS genes? Does it make a phenotypic difference how many and which of these genes are involved in the disease? Presumably, BBS involves mutations at one locus, and the modifying locus can be any one of the other five loci. Does a similar pattern of inheritance occur in other diseases? There are multiple examples of such genetic behavior in the fruit fly *Drosophila* and in other model organisms. For example, mutation of both copies of the fruit fly *fasciclin I* gene, which encodes a cell adhesion protein, results in viable offspring with no morphological defects. However, when this mutation is combined with mutation of the tyrosine kinase *Abl*, defects in the axons of the nervous system become apparent (*6*). Another example is provided by the enhancer split transcription factor complex, E(spl)-C, in *Drosophila*. Loss-of-function mutations in one allele of individual E(spl)-C genes result in a viable individual, and there is no detectable phenotype. Additional loss-of-function mutations in other E(spl)-C genes are required for a phenotype to be present—in this instance, hyperplasia of the nervous system. Several genes of the E(spl)-C encode basic helix-loop-helix transcription factors that can form homo- and heterodimers that repress transcription of genes important for neurogenesis (*7*, *8*).

There are also examples of similar phenomena in mammals. In mice, the mutant gene causing the disorganization (Ds) phenotype has a penetrance (frequency of observing an affected individual with the mutation) ranging from almost 0 to 89%, depending on the strain of mouse (*9*). In humans, there is a dominant modifier of the nonsyndromic deafness gene *DFNB26*. Most individuals who have mutations in both copies of *DFNB26* on chromosome 4q31 develop hearing loss, but some members of a family did not owing to expression of a dominant modifier gene on chromosome 7. In β-thalassemia, the expression of HbF (fetal hemoglobin) modifies the severity of the disease phenotype (*10*). In spinal muscular atrophy (SMA), a neurodegenerative disease, there are families in which siblings lack both the SMA gene *SMN1* and have identical copy number of the known phenotypic modifier gene *SMN2* yet develop completely different phenotypes—severely

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affected versus very mild or normal (*11*). A difference between this situation and that reported for BBS is the apparent frequency of modification. In SMA, these families are the exception, whereas in BBS, it appears that in most cases one needs three mutant BBS genes to obtain a phenotype, and it is unclear whether BBS can develop with just two allelic mutations. Given the frequency of two-gene involvement in BBS, the ease with which linkage mapping was applied to identifying the six loci may seem surprising (*5*). One would expect to see some segregation distortion, which has been reported in SMA but not in BBS. It is perhaps fortunate that haplotype association has been used to narrow the region containing the BBS genes. It will also be of interest to know the frequency of BBS mutations in the population because a two-gene model for this disorder would predict a higher frequency of single-gene BBS mutations. In the near future, we should know whether two-gene mutations are always required in BBS, the frequency of the alleles, and how each of the genes contributes to the phenotype. It will be particularly intriguing to determine if there are gene modifiers or genetic loci that specifically predispose BBS patients to hypertension and diabetes.

The examples given so far are for recessive conditions, but phenotypic modification also occurs in dominant disorders. An example is familial adenomatous polyposis (APC), a disease characterized by numerous intestinal polyps that predispose the individual to colon cancer. In the APC^{min} mouse model of this disease, the *APC* gene is mutated but the number of polyps varies depending on the genetic background of the mouse. A semidominant modifier gene, *Mom1*, accounts for 50% of the genetic variance in polyp number (*9*). In strains with reduced polyp number, activity of the secretory phospholipase A2 (Pla2g2a) is normal. Pla2g2a is part of the prostaglandin synthesis pathway, leading to the realization that drugs affecting this pathway could be used to reduce polyp number. Although modifier genes and susceptibility genes do complicate the genetic understanding of disease, they also provide additional targets against which drugs can be directed. For example, high-throughput drug screens are currently being performed to identify compounds that activate the *SMN2* gene, which is intact in all SMA patients and is known to modify the phenotype. Can the BBS phenotype be rescued by stimulating expression of the remaining functional allele of the modifier gene? Will this approach be valuable in more common multifactorial disorders where stimulation of expression of a modifier may prevent the phenotype?

Three of the six possible genes mutated in BBS have been identified: *BBS2* encodes a protein of unknown function (*12*); *BBS6* encodes a protein with homology to TriC chaperones that form a complex of nine related proteins (*13–15*); and *BBS4* encodes a protein with homology to O-linked *N*-acetyl glucosamine transferase (*16*). The fact that any of five BBS loci can act as modifiers implies some form of interplay between the six genes, or more specifically, between their products. But how does this modification of penetrance work? Do the BBS gene products interact directly or affect the same biochemical pathway? The next step in understanding whether and how these proteins interact will depend on elucidation of their biochemistry. The proteins encoded by the modifier genes, in particular the BBS4 glucosamine transferase, hint that post-translational modification of other BBS proteins may be involved in the disease phenotype, but this is far from clear. BBS is an excellent model not only for more common multifactorial diseases, but also for disorders where the mode of inheritance is complex.

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PERSPECTIVES: ECOLOGY AND EVOLUTION

The *Inga*—Newcomer or Museum Antiquity?

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Writing in 1878 (*1*), the great biogeographer and evolutionary biologist Alfred Russel Wallace suggested that the high species diversity of the tropics could be accounted for by the greater age of tropical environments—providing more time for species to accumulate—compared with environments of temperate regions. After all, parts of lowland South America have been draped in tropical vegetation for over 100 million years (*2*), whereas the distribution of temperate forests has tracked the push and pull of glaciers. A century after Wallace, G. Ledyard Stebbins (*3*) introduced the *museum hypothesis*, providing a name for the more refined idea that "plant communities that have suffered the least disturbance during the last 50 to 100 million years...have preserved the highest proportion of archaic forms." Stebbin's view challenged the *cradle of diversity* hypothesis that had largely supplanted Wallace's early notion of the importance of time for explaining tropical species diversity. The cradle of diversity hypothesis held that the tropics are a crucible of evolution in which adaptive complexes arise owing to the biotic complexity of tropical forests. The explosive radiation of New World orchids, for example, is partly due to the group's intricate coevolutionary interactions with pollinators (*4*). The idea that high rates of tropical speciation, rather than age or reduced rates of extinction, contribute to tropical forest diversity gained added prominence with the publication of the *refugia* model in the 1960s (*5*). This model posited that allopatric divergence (that is, divergence of very similar organisms that cannot interbreed due to geographical isolation) in fragmented ice-age forests acted as a species pump, supporting the prediction that tropical species diversity is a recent event. So, the question still remains: is most tropical diversity ancient or new? To unravel the answer, Richardson and colleagues (*6*) have undertaken a molecular systematics study of the tropical tree genus *Inga*, which they report on page 2242 of this issue.

The legume genus *Inga* is composed of roughly 300 species that range from central Mexico to northern Argentina. Richardson and co-workers indicate that

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