

## The Land Between Mendelian and Multifactorial Inheritance

Burghes et al discuss the concept that genetic disorders can often be thought of as attributable to Mendelian and/or multifactorial triats. However, we now must consider other possibilities in classifying certain genetic syndromes. One such category has been classified as *triallelic inheritance*. The Bardet-Biedl syndrome, as published by Katsanis et al, is tagged as such. This article prompts a perspective commentary on genetics by Burghes et al.<sup>1</sup>

Although there has been spectacular success in identifying genes responsible for Mendelian inherited disorders, finding *susceptibility* genes involved in multifactorial diseases has been a struggle. How multiple genes interact to give the final phenotype of a multifactorial disease and what we might expect, remains an enigma. The land between Mendelian and multifactorial inheritance is inhabited by genes such as *modifier genes* and *redundant genes* that have many effects on the developing phenotype. Understanding the mode of action of these will help in determining how *susceptibility genes* may interact to give rise to a multifactorial phenomena.

Katsanis et al<sup>2</sup> report that mutations in two genes, rather than one, cause Bardet-Biedl syndrome (BBS). Katsanis points out that six BBS loci exist in humans. Three of these have been identified (BBS2, 4, and 6); the other three have not, as yet. Mutated genes have been identified in BBS2, BBS4, and BBS6 genes. Katsanis et al describe 11 subjects, out of a group of 163, who were genetically characterized with heterozygous or compound heterozygous mutations in BBS2, and three families with normal individuals who had the same two mutated BBS2 alleles. In three pedigrees the affected BBS patient had mutations of both BBS2 alleles and a mutation in one BBS6 allele. In one family the affected BBS patient had a mutation of one BBS2 allele and mutations in two BBS6 alleles. Thus, in four families mutations in three BBS alleles were demonstrated and apparently necessary for expression of the disease phenotype. Katsanis proposed that BBS may not be a single gene recessive disease, but a complex trait requiring three mutant alleles to manifest the phenotype. The phenotype of BBS includes pigmentary retinopathy, polydactyly, obesity, developmental delay, and renal defects. The figure illustrates the complex inheritance in Bardet-Biedl syndrome.

### References

1. Burghes AHM, et al. *Science* 293:2213-2214,2001.
2. Katsanis N, et al. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. *Science* 293:2256-2259,2001.

**Editor's Comment:** The concept that mutations of genes on more than two alleles may be necessary for expression of a disorder is at odds with classical Mendelian transmission through dominant or recessive mechanisms, but is not incompatible with our understanding of diseases that appear to require multiple genetic and/or environmental factors for expression (e.g., diabetes mellitus, obesity, spinal muscular atrophy). Inasmuch as the majority of patients with BBS and mutations in BBS2 had normal BBS6, it is likely that these investigators will search for mutations in BBS4 (and BBS1 and 3 when they are identified) in this large group of BBS subjects. Since the phenotype of BBS is consistent despite the genotype, one suspects that the various BBS loci identified will be linked to one another in a metabolic process(es) that when interrupted leads to the disorder. Incidentally BBS6 is also mutated in patients with the McKusick-Kaufman syndrome of congenital heart disease, polydactyly, and transverse vaginal septum leading to hydrometrocolpos in females.

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