This Month in the *Journal*

If beauty is really to be found in the beholder's eye—or, more generally, in the sensory systems of the perceiving subject—it seems that heritable differences in the function of our sensory organs must influence how we experience, appreciate, and respond to our surroundings. Three articles in this issue discuss the genetics of human perception, highlighting both the physiological and behavioral differences seen between individuals and the biochemical and developmental similarities among the different senses. Wissinger and Sharpe (p. 1257) describe the basis of color vision and its genetic variability. They review the expression and function of rod pigment genes, and they conclude by discussing a family of cyclic nucleotide-gated channel genes. One of these genes recently has been found to underlie total color blindness in people, and another is essential for olfactory perception in diverse animal species. Fritzsch and Beisel (p. 1263) recount the parallel development of sensory neurons in the ear and in taste buds. They focus especially on the Trk family of neurotrophin receptors, which they have studied extensively in targeted mouse lines, and they review some of the similar developmental abnormalities seen in humans and in mouse models of deafness. Finally, Tepper (p. 1271) discusses the differences in people's ability to perceive the bitterness of various foods—and the relation of this phenotype to other, seemingly unrelated, gustatory traits, such as sensitivity to the hotness of spicy flavors and the mouth feel of fatty substances.

Phenotypes and Genotypes in PBD, *by Chang and Gould* **(***p. 1294***)**

Peroxisome-biogenesis disorders (PBDs) can be caused by mutations in at least nine genes, which have been defined by complementation tests in cell culture. The range of clinical symptoms, from milder forms of the disease to the most severe, are seen in each of these complementation groups, and all of these genes seem to participate in a common intracellular pathway that allows protein import into peroxisomes. Chang and Gould show here that severe cellular phenotypes—as judged by the complete failure of cells to direct proteins into this organelle—arise in complementation group CG3 when both alleles of the *PEX12* gene carry premature termination codons; this class of genotypes is generally associated with the severest form of clinical PBD. Milder cellular and physiological effects arise when missense alleles permit some import. However, a 2-bp deletion that occurs near the *5′* end of the gene provides an interesting exception. This allele causes an unexpectedly mild phenotype, probably because ribosomes initiate translation at one of two internal methionine codons, hence bypassing the more *5′* termination codon introduced by the deletion.

FKHL7 ***Mutations in IRID1 Patients,*** *by Mears et al.* **(***p. 1316***)**

IRID1, one of numerous autosomal dominant glaucoma loci, is associated with malformations of the anterior segment–angle structures. This developmental aberration appears to restrict flow of the aqueous humor, leading to increased intraocular pressure and, eventually, blindness. Mears et al. report that the gene underlying this defect is a member of the forkhead/winged-helix family of DNA-binding proteins, a class of transcriptional regulators that control morphogenesis in many tissue types and in both vertebrates and invertebrates. Having restricted the IRID1 locus to a 3.9-cM region distal on 6p, the authors sequenced 120 kb of DNA from a promising bacterial-artificial-chromosome *FKHL7* gene, which, they found, is mutated in three probands with glaucoma linked to 6p25. Their inability to find mutations in other families, as well as some phenotypic differences among their patients, suggest that this chromosomal region may harbor at least one other gene related to intraocular pressure and blindness. Mears et al. have also created a targeted mouse mutation in the homologous gene, *Mf1*. They show here that this gene, whose homozygous deletion leads to both brain and eye defects, is expressed in periocular tissue in the mouse.

Mutations in the **UROD** ***Gene Causing f-PCT,*** *by Mendez et al.* **(***p. 1363***)**

Homozygous defects in the *HFE* gene cause the iron-storage disease hemochromatosis, but, as Mendez and coworkers now show, even a single defective allele may have subtle effects on iron metabolism. These authors have followed the development of familial porphyria cutanea tarda (f-PCT), a skin disorder associated with haploinsufficiency in the gene for uroporphyrinogen decarboxylase (*URO-D*), a key enzyme in heme biosynthesis. By sequencing the compact *URO-D* gene as a single PCR product, Mendez and colleagues identified six novel mutations—including an insertion, a deletion, and a splicing-defective allele, as well as three missense mutations that appear to encode unstable or relatively inactive

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products. Of the 10 f-PCT individuals whom these authors studied, 5 also carried missense mutations in *HFE,* in heterozygous or homozygous form. This unusual prevalence of *HFE* mutations suggests that partial loss of *HFE* function can precipitate PCT in people predisposed to the condition. The *HFE* H63D substitution, whose effect in hemochromatosis has been difficult to confirm, was particularly common in this group, indicating that, although in itself it is generally innocuous in heterozygotes, this mutation can alter iron storage.

ITGB4 ***Mutations in EB-PA,*** *by Pulkkinnen et al.* **(***p. 1376***)**

Integrins are a large family of versatile heterodimeric receptors for extracellular matrix component. Despite their involvement in adhesive interactions in virtually all cell types, loss of expression of many integrin subunits is compatible with fetal development. The $\alpha 6\beta 4$ integrin dimer, a receptor for some forms of laminin, localizes to hemidesmosomes in squamous epithelia such as the skin, and it is required to link the skin-cell intermediate-filament cytoskeleton to the basement membrane. Complete loss of either $\alpha 6$ expression or $\beta 4$ expression leads to epidermolysis bullosa with pyloric atresia, presenting with fragile skin and with atresia in the upper gut. As with a corresponding genetic defect that occurs in targeted mouse mutants, this autosomal recessive blistering disorder is usually fatal within weeks after birth. Mild forms of the disease may also result from mutations in either gene. Pulkinnen et al. have searched systematically for mutations in the two integrin genes in five unrelated families. All five probands were homozygotes or compound heterozygotes for *ITGB4* mutant alleles, but all three who survived early infancy carried missense alleles, which are presumed to be expressed and to retain some function.

X Inactivation in Barth Syndrome Carriers, *by Ørstavik et al.* **(***p. 1457***)**

Ørstavik and coworkers have followed the patterns of X inactivation in females from six families with Barth syndrome, an X-linked developmental disorder that is usually fatal in infancy or childhood in males but that has no overt phenotype in carrier females. In all families, most or all of the carriers showed some degree of skewing of their X-chromosome activity profile. Ørstavik et al. argue that this is likely to reflect somatic selection against cells that inactivate the wild-type copy of the *BTHS* gene, rather than chance events or a direct effect on the X-inactivation system. The variable degree of skewing and the fact that extreme patterns of skewing do not appear to become more common in these families as women age may suggest that expression of *BTHS* is primarily advantageous for cell survival at an early point in female development.

Association between Genetic Markers and Disease, *by Schaid and Rowland* **(***p. 1492***)**

The transmission/disequilibrium test compares parental genotypes at candidate marker loci with those of affected offspring, so it avoids complications that derive from ethnic differences between cases and controls. Still, the need for parental DNA samples limits the application of the method, and several groups have devised statistics that allow other control groups, particularly siblings, to be used instead. Schaid and Rowland now introduce a general approach that simultaneously accommodates data from various control groups—parents, siblings, and unrelated individuals. By this method, the effects of population stratification in the unrelated control group can be measured, and spurious associations that are based on departures from Hardy-Weinberg equilibrium can be avoided. The authors discuss the differences in statistical power that are intrinsic to the use of each class of control.

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