This Month in the *Journal*

With this issue, we inaugurate "Human Genetics '97," a collection of invited reviews and editorials that cluster around a single broad theme. This month's focus is on behavioral genetics. We feature an ASHG policy statement on the topic (Sherman et al., p. 1265), as well as reviews of recent advances in mood disorders (Reus and Freimer, p. 1283), childhood psychiatric disorders (Smalley, p. 1276), and sleep disorders (Mignot, p. 1289). In coming months, this series will feature articles on gene regulation; the use of large-mammal model systems to approach human genetics; gene therapy; and other areas of interest to human geneticists.

Linkage of a High-Bone-Mass Trait, *by Johnson et al. (p. 1326)*

Bone mineralization density (BMD) is a quantitative trait that is strongly influenced by age, sex, and environment. Although twin studies have demonstrated that BMD is also profoundly affected by heredity, the genetic control of BMD is not well understood. Johnson et al. examined a healthy young woman who appears to have inherited high BMD as an autosomal dominant trait through her mother's family. Linkage analysis within this family suggests that a high-penetrance gene that maps within a 30-cM interval on 11q contributes to high BMD. The mapping of this putative quantitative-trait locus near a gene for osteoporosis pseudoglioma syndrome raises the possibility that the two traits, one with high and the other with low bone density, are allelic. See the commentary by Whyte in this issue.

Analysis of the* FMR1 *Promoter, *by Schwemmle et al. (p. 1354)*

Fragile X syndrome may arise through loss of expression of the *FMR1* gene, typically as a consequence of an expansion in a CGG trinucleotide in the *FMR1* promoter. Earlier analysis of this promoter used methylation-sensitive restriction enzymes to show that CpG sequences are hypermethylated in cells of affected individuals. Schwemmle et al. have now extended this observation in several respects. They applied ligation-mediated PCR to confirm that, in immortalized fibroblasts taken from affected individuals, methylation is essentially complete at all sites examined. However, they find no evidence for such methylation in asymptomatic people, including transmitting individuals with expanded CGG repeats. The authors have also used in vivo footprinting to show that, accompanying this increase in methylation, binding of factors to four sites in the promoter region is lost. Schwemmle et al. suggest that methylation abolishes expression by interfering with the interaction of transcriptional activators with the *FMR1* promoter.

Promoter Duplication of Human mtDNA, *by Hao et al. (p. 1363)*

Here, Hao et al. report on their cell-culture studies on a 260-bp duplication that affects the major heavy- and light-strand promoters in the mitochondrial genome. This duplication has been described before, and several groups, including these authors, speculated that it might be a pathological variant. However, working with transmitochondrial cybrids—cloned cells in which the only mtDNA is derived from other cells—Hao et al. have now examined oxidative phosphorylation and mtDNA replication in the presence of this duplication. By both of these measures, cells in which >99% of mtDNA carries the duplication appear normal. These findings do not rule out an effect of the duplication in some specialized cells, but they strengthen the argument that the duplication represents a neutral polymorphism.

Molecular Basis of Acute Porphyria, *by Puy et al. (p. 1373)*

Puy et al. explore the benefits of DNA-based diagnosis of acute intermittent porphyria (AIP), a heme-biosynthesis defect that arises from deficient expression of porphobilinogen deaminase (PBD). The established approach of assaying erythrocytes may fail for several reasons. For instance, some alleles affect only nonerythroid cells. Also, many individuals who are apparently at risk on the basis of genotype show normal PBD levels and remain asymptomatic. Puy et al. used denaturing gradient gel electrophoresis (DGGE) to study 129 French AIP families. They define mutations, 33 of them novel, in 109 of these families. Of the biochemically diagnosed families, only 12 lack an evident mutation in *PBD*. The authors argue that the DGGE method is well suited to presymptomatic identification of AIP individuals and particularly, AIP carriers.

***Mutations in Duplicated Region of* PKD1,** *by Peral et al. (p. 1399)*

Mutations in the *PKD1* gene frequently lead to renal failure, a consequence of polycystic kidney disease. Numerous mutations at the 3′ end of the gene have been characterized in *PKD1* families, but the 5′ end of the gene, which resides in a tandemly repeated portion of 16p, has not been amenable to mutation analysis. Peral et al. describe a method, based on reverse-transcriptase–PCR (RT-PCR), by which 12 of the 32 previously un-

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characterized 5′ exons can be amplified without contamination from upstream sequences. The initial amplification product is then characterized at the sequence level or by the protein-truncation test. This approach yielded 11 mutations among 11 familial or sporadic cases of PKD. Despite this success, it clearly represents only a partial solution to the problem, because it can only be applied to alleles that are expressed sufficiently to be detected by RT-PCR, and because the 20 5′-most exons are excluded from this analysis.

SMN^T *and* SMN^C *Gene Copy Number,* *by McAndrew et al. (p. 1411)*

Spinal muscle atrophy (SMA) is another disease in which molecular diagnosis is complicated by sequence duplication in the genome. Two highly homologous genes, *SMN^C* and *SMN^T*, reside on 5q; mutations in *SMN^T* are specifically associated with SMA. Quantitative competitive PCR has been employed to identify *SMN^T* deletions, but previous studies have measured the ratio of *SMN^C* and *SMN^T* copies. As McAndrew and colleagues now show, however, this ratio may be misleading, because the number of copies of *SMN^C* varies among SMA individuals. Instead, this group has developed a competitive PCR method that normalizes copy number of *SMN^T* to that of an unlinked and stable genomic fragment. They show here how they used this method to detect a twofold loss of *SMN^T* signal in a compound heterozygote with a deletion affecting one copy and with a point mutation in the remaining copy of the gene.

Mapping of the Urofacial Syndrome Gene, *by Wang et al. (p. 1461)*

Wang and co-workers have applied two powerful linkage strategies to map the gene for urofacial syndrome. This syndrome presents with inverted facial musculature and a variety of urinary-tract abnormalities that predispose to infection and, hence, to kidney disease. Working with both consanguineous and nonconsanguineous families that exhibit this autosomal recessive disorder, Wang et al. have performed whole-genome scanning to find markers that are homozygous specifically in the patient set. At the same time, they pooled genomic DNA from patients and from obligate carriers and analyzed these for quantitative differences in allele distribution that suggest linkage. After examining a total of only 24 samples, they report that the homozygosity and the pooling methods both indicate linkage to 10q, probably within a 1-cM region.

Complementation of NBS by Chromosome 8q, *by Matsuura et al. (p. 1487)*

The Nijmegan breakage syndrome (NBS) presents with a complex of developmental abnormalities and a cellular phenotype of radiosensitivity and cell-cycle misregulation, a phenotype reminiscent of severe combined immunodeficiency (SCID). Matsuura and co-workers have revisited some earlier cell-fusion studies that seemed to indicate that there were at least two NBS complementation groups. Using isolated chromosomes and chromosomal fragments delivered in minicells, these authors show that a region of 8q complements NBS in all cells, suggesting that the defect is homogeneous. The gene associated with human SCID maps to an 8q region distinct from this NBS-complementing locus.

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