This Month in the *Journal*

In this month's issue, we feature four reviews on the genetics of neurological development and disease. Jiang et al. (p. 1) begin the series by discussing the discovery of the imprinted *UBE3A* gene as the causative gene in Angelman syndrome (AS), the development of mouse models of AS, and the regulation of *UBE3A* imprinting. AS can occur through a remarkable number of genetic mechanisms, and Jiang et al. introduce a unifying nomenclature to describe them all. Sisodia et al. (p. 7) and Giulian (p. 13) both are concerned with the development of Alzheimer disease (AD). Sisodia et al. (p. 7) discuss the presenilins, intracellular proteins that are implicated in the pathway that generates amyloidogenic peptides from the amyloid-precursor protein. Remarkably, presenilins influence the packaging of specific proteins into secretory vesicles in diverse organisms. Giulian describes the role of brain microglia in the death of hippocampal neurons, work that begins to make sense of the relationships between cognitive decline, amyloid deposition, and apolipoprotein E polymorphisms. Fox and Walsh (p. 19) discuss periventricular heterotopia, a developmental disorder in which neurons lack the cytoskeletal protein filamin-1 and fail to migrate. This protein has also been studied in the slime mold *Dictyostelium discoideum*, the subject of Saxe's review (p. 25). Saxe reviews the merits of this simple model eukaryote for human disease genes, studying, in particular, the Wiscott-Aldrich syndrome gene, *WASP*.

Mutation Detection in the* PKD1 *Gene, *by Thomas et al.* (*p. 39*)

Loss-of-function alleles of the *PKD1* gene cause polycystic kidney disease, a dominantly inherited progressive renal disorder that also causes cysts in the liver and pancreas. Somatic second hits may promote cyst formation by abolishing residual expression of *PKD1* in isolated domains of each of these organs. Because the 5′ end of *PKD1* is present in nearly identical form in multiple genes, only the 3′ end of the gene has proved amenable to systematic mutation analysis. The first 15 exons have been particularly difficult to screen, but now Thomas et al. have identified in the gene a short region that diverges from the other homologues, so that *PKD1*-specific PCR primers can be designed to amplify this region from patients' DNA. Using long-range PCR, Thomas and colleagues amplify a 13-kb genomic fragment that covers exons 2–15, and they identify eight likely pathological mutations in this portion of the gene, by sequencing this product from 24 unrelated individuals with the disorder.

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The* GM2A *Gene Structure and Novel Mutation, *by Chen et al.* (*p. 77*)

Premature-termination codons (PTCs) have two unexpected effects on steady-state mRNA distributions, as they are measured by northern or reverse transcription–PCR analysis. First, they generally cause the affected mRNA to be unstable. Second, in some instances, they permit aberrantly spliced forms of the mRNA, in which the PTC is excised from the mature message, to accumulate in the cytoplasm. The latter effect, in particular, has been taken as evidence for an intranuclear surveillance mechanism that alters the splicing pathway, in response to breaks in a pre-mRNA's open reading frame. However, Chen and coworkers now provide support for an alternative model that does not require nuclear factors to be sensitive to the mRNA reading frame. Working with cells from a child with severe GM2 gangliosidosis, Chen et al. trace the defect to a nonsense mutation in the second exon of the *GM2A* gene, and they show that GM2A mRNA is expressed in a shorter form with an in-frame deletion that removes exon 2. Although this splicing form is not readily detected in preparations from normal cells, the authors use a specific restriction enzyme to prevent the full-length sequence from being amplified, and they show that it is indeed expressed at low levels in normal—as well as the affected individual's—cells. Therefore, the presence of aberrant splicing forms in such cases may reflect the instability of the PTC-containing mRNA, rather than a direct effect on the splicing pathway.

***CD Breakpoints ⩽1 Mb from* SOX9** *by Pfeifer et al.* (*p. 111*)

SOX9 encodes a transcription factor related to the testis-determination factor SRY, and defects in *SOX9* cause an autosomal dominant developmental syndrome, campomelic dysplasia. This condition apparently results from haploinsufficiency for SOX9 expression in developing bones and testes, and it leads to skeletal dysmorphologies and, often, sex reversal. Although CD is often caused by point mutations in *SOX9,* translocations and inversions that break upstream of the gene can also cause the disease. Pfeifer and colleagues have mapped the breakpoints in 14 such cases, and they report here that the lesions may occur at distances from 50 kb to nearly 1 Mb upstream of the gene. The authors consider the

possibility that these distant breakpoints actually disrupt a different gene, but, in sequencing around the affected regions, they find no support for this notion. More likely, Pfeifer et al. indicate, the gene is under control of an exceptionally long regulatory domain, or else the translocations drive the gene into a heterochromatic state in which it is only weakly expressed.

Cherubism Gene on Chromosome 4p, *by Mangion et al.* (*p. 151*)**; *Mapping of the Gene for Cherubism,*** *by Tiziani et al.* (*p. 158*)

Another long-studied skeletal disorder, cherubism, specifically affects the bones of the jaw, which develop enlarged, poorly calcified lesions in childhood that often regress at puberty. The condition owes its name to the resemblance of the affected children to the full-faced cherubs of Renaissance paintings. In this issue, two groups link the condition to 4p16, in the vicinity of the *FGFR3* gene. Mangion et al. confine the cherubism locus to a 3-cM interval extending to the telomere of 4p. Tiziani et al. define a much larger critical region that appears to exclude the two most telomeric markers on 4p, so these data could be used to narrow the region of interest in the other report. Both groups cite *FGFR3* as a candidate gene, noting that mice that lack *Fgfr3* expression exhibit generalized bone overgrowth. If this gene is indeed involved in cherubism, it will be important to determine how the effects of the mutation are limited, spatially and temporally.

Sequence Diversity in Human Genes, *by Cambien et al.* (*p. 183*)

Cambien and colleagues look toward postgenomic research in this exploration of large-scale sequence diversity. For mapping genes of modest effect, intragenic sequence variation may be at least as useful as randomly distributed single-nucleotide polymorphisms, but relatively little is known about the extent of normal variation in most coding and regulatory sequences. Cambien et al. begin to address this question with 36 genes that may be considered candidates for cardiovascular disease. The authors use SSCP to discover 164 polymorphisms within this 135-kb subgenome, and they screen 750 healthy Europeans for each of these variants. They report extensive linkage disequilibrium among loci within a gene, a finding that encourages them to embark on association studies, in the belief that disease-related variants, too, are likely to be in disequilibrium with these markers.

Expanded CAG Repeats in General Populations, *by Deka et al.* (*p. 192*)

Repeat-expansion detection (RED) is a strategy for finding unstable repeats that might, like the CAG trinucleotide repeats underlying various inherited ataxias, cause intergenerational anticipation in human diseases. Unfortunately, two loci, ERDA1 on 17q and SEF2-1 on 18q, contain long and highly unstable CAG repeats. Spurious associations between disease phenotypes and changes in CAG repeat length at these loci greatly complicate the detection of pathological repeat expansions, leading some critics to declare that RED is dead. Deka and coworkers have followed the distribution of CAG repeat lengths and the meiotic instability of one of these troublesome loci. In ERDA1, maternal transmission favors expansion, and paternal transmission favors contraction, of the repeat, and the presence of interruptions in the CAG repeat allows an intermediate-length repeat to be transmitted stably across generations. Deka et al.'s finding that repeats in the range of 10–40 triplets are no more unstable than other microsatellite repeats and that some populations are relatively free of large, unstable alleles may permit the use of RED in selected groups of subjects.

Detection of Parent-of-Origin Effects, *by Weinberg* (*p. 229*)

Parent-of-origin (PO) effects occur when a child's risk of exhibiting a genetic disease is influenced by whether a disease allele was derived from the mother or the father, as when genes are imprinted. Other aspects of the parental genotypes can also influence a child's phenotype. In particular, maternal effects, understood as intrauterine environmental influences that depend on the mother's genotype, do not require that any specific disease gene be transmitted to the child. Two common statistical tests used for detecting linkage, the transmission/disequilibrium test and the likelihood-ratio test (LRT), have been adapted to test for PO effects. Here, Weinberg discusses limitations of these approaches, including the difficulty in distinguishing between maternal effects and paternal imprinting. Weinberg suggests two additional tests, the PO-LRT and the parental asymmetry test (PAT), and she compares them with the two existing methods, using simulation. Based on simulations, the PO-LRT proves to be the most generally valid of the four tests, but it is less powerful than the others, so the PAT is to be preferred when maternal effects can be discounted.

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