This Month in the *Journal*

Three reviews in this issue focus on different aspects of human mitochondrial genetics. Chomyn (p. 745) discusses the molecular biology of myoclonic epilepsy with ragged-red fiber (MERRF), one of the best understood of the mitochondrial diseases. She describes methods for reconstituting cells with normal or MERRF mitochondria, as well as the insights that these methods provide into genetic complementation between mtDNAs. Poulton et al. (p. 752) consider the mitochondrial bottleneck in human development, and they discuss recent work that may allow genetic counselors to assess a mother's risk of transmitting mitochondrial diseases. Parker and Swerdlow (p. 758) describe abnormal features of mitochondrial electron transport in people with Parkinson disease. Although this condition is widely believed to occur sporadically, Parker and Swerdlow argue that it is unlikely to have a strictly environmental etiology, but it may arise from mutations in mtDNA.

Mutations in Connexin 26* (GJB2),** *by Kelley et al.* **(p. 792***)**

DFNB1 is a nonsyndromic form of hereditary deafness caused by loss of functional gap junctions in cochlear cells. Connexin 26, the product of the *GJB2* gene, may be required for ion transport during auditory-signal transduction. Kelley et al. have surveyed 58 families in which nonsyndromic deafness segregates as an autosomal recessive trait, and they find that nearly a third of these carry mutations in *GJB2*. The authors report six novel mutations, bringing the total number of deafness alleles in this gene to 14. One allele, 101T→C, which was found in this group, had been claimed to underlie dominantly inherited form of deafness, but in the present study this variant was found at significant levels in control populations, suggesting that it might be a neutral polymorphism. Kelley et al. attempt to reconcile these data, speculating that specific genetic interactions are needed to reveal the dominant effect of this point mutation.

COL11A1 *Defect in Marshall Syndrome,* *by Griffith et al.* **(***p. 816***)**

Marshall syndrome and Stickler syndrome refer to two closely related skeletal dysplasias that are distinguishable—at least according to some authors—because they lead to different facial features and because cleft palates are more common among Stickler individuals, whereas hearing loss is more common in Marshall syndrome. The genetic relation between the conditions has been uncertain, but the decades-old debate between lumpers and splitters may be ended by this report from Griffith and colleagues. Stickler syndrome had been associated with mutations in any of the three collagen genes, *COL11A1*, *COL11A2*, and *COL2A1*, whose products make up interstitial type XI collagen. Griffith et al. have ascertained a three-generation family with Marshall syndrome, and they show that a novel splice-site mutation segregates with the disorder, demonstrating that Marshall syndrome is allelic with at least one form of Stickler syndrome.

Dodecamer Repeat Expansion in* EPM1,** *by Lalioti et al.* **(p. 842***)**

Lalioti and coworkers reported last year that the cystatin B gene, *CSTB*, encoding a secreted inhibitor of cysteine proteinases, is mutated in the autosomal recessive disorder, progressive myoclonus epilepsy (EPM1). They identified in disease alleles of *CSTB* an unusual set of promoter mutations in which a 12-bp G- and C-containing repeat had expanded beyond the two to three tandem copies found in controls. Now this group has developed a PCR-based method for measuring these repeat lengths precisely, and they find that copy number varies dramatically within affected families. Hence, repeat length is unstable in the germ line, but they find no evidence for instability in somatic cells. Unlike many known unstable-repeat disorders, no correlation emerges between repeat length and age at onset, as long as the tract is above a threshold size of ~30 repeats. It will be interesting to learn whether 12-mer repeats above this size undergo a conformational transition, such as to Z-DNA, under physiological conditions.

Pycnodysostosis Caused by Paternal UPD1, *by Gelb et al.* **(***p. 848***)**

Uniparental disomy (UPD) can uncover recessive defects in either of two ways: by creating a homozygous genotype or by inactivating gene expression through imprinting. Gelb et al. now report a case of UPD that leads to pyknodysostosis, a dysplasia that presents with short and fragile bones and with a distinctive set of facial features. Here, the affected boy carries two paternally derived copies of chromosome 1, including the gene for cathepsin K, which is implicated in this disorder. He is homozygous for a missense mutation that his father car-

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ries in heterozygous form. Other chromosome 1 markers are consistent with UPD, but only the centromeric markers on this chromosome are homozygous, suggesting partial isodisomy. On the basis of these data, the authors reconstruct the paternal nondisjunction that probably led to the observed chromosome 1 genotype. They also note that, because the boy is free of other developmental disorders, chromosome 1 is unlikely to carry any paternally imprinted genes.

Genetic Heterogeneity in X-linked CSNB, *by Boycott et al.* **(***p. 865***)**

Congenital stationary night blindness (CSNB) is a clinically heterogeneous eye disorder. In its "complete" form, X-linked CSNB presents with a profound failure of dark adaptation in rod cells, a process that is only mildly and variably affected in families with "incomplete" CSNB. The two forms can also be distinguished by electroretinogram patterns induced by dim blue light. Boycott et al. use these criteria to follow linkage of complete and incomplete CSNB in 32 affected families, 18 of which are newly ascertained. Drawing on their own genotyping data and published data, Boycott et al. confirm that both forms of the disease map to Xp11, but critical recombinations allow them to define nonoverlapping critical regions for the two conditions.

A 46,XX/46, XY Chimeric Hermaphrodite, *by Giltay et al.* **(***p. 937***)**

Giltay et al. describe an unusual case of true hermaphroditism—that is, the presence of both ovaries and testes in a single individual. In this case, a child with normal male external genitalia and with one normal testis was born with a second gonad that had histological features of both ovaries and testes. The boy's somatic tissues are likewise a mixture of karyotypically normal male and normal female cells. Analysis of autosomal and sex-chromosome markers indicates that a single ovum and two sperm developed into this mosaic individual, and the authors suggest the probable events along this path.

Using Neural Networks to Determine Disease Status, *by Falk et al.* **(***p. 941***)**

Artificial neural networks are computer programs that can be "trained" to make distinctions between classes of items even when no algorithmic method for doing so can be specified in advance. A natural application of this technique is in the diagnosis of complex clinical syndromes. Here, Falk et al. describe their experience in training a neural network to diagnose limb-girdle muscular dystrophy type 1A (LGMD1A) on the basis of a limited list of clinical criteria. They find that, in 98% of cases in which physicians could make a clear diagnosis of LGMD1A, the trained network made the same assignment. Furthermore, the network offered ambiguous assignment in some of the same cases that were troublesome to diagnosticians. A crucial question is whether neural networks can be more reliable—or more discerning—in their diagnoses than are their human "counterparts." Falk et al. supply a readable introduction to the theory of neural networks, as an appendix to their article.

A Log-Linear Model for Case-Parent Triads, *by Weinberg et al.* **(***p. 969***)**

Weinberg et al. introduce a novel analytical method for detecting linkage disequilibrium. Like the transmission/disequilibrium test (TDT), their method starts with genotype data from sets of three people, an affected individual and his or her parents. Unlike the TDT, however, the method of Weinberg et al. proceeds by specifying the "mating type"—that is, the combined parental genotype of the parents; the likelihood of the affected offspring's genotype is determined, conditioned on this mating type. Weinberg and colleagues argue that their approach works even when inheritance does not conform to Mendelian rules. Thus, sophisticated biological models, such as gametic imprinting or maternal (intrauterine environment) effects, can be accommodated in this analysis but not by the TDT.

Genetic Determinism, *by Condit et al.* **(***p. 979***)**

It is widely claimed that the advent of molecular genetics promoted a "determinist" view of people's abilities and weaknesses. Condit and colleagues have analyzed journalistic writing sampled from the past 80 years, trying to identify trends in the frequency of statements that indicate genetic, rather than environmental, bases for human traits. They find that, over many decades, the level of genetic determinism in at least this portion of public discourse has been relatively constant, suggesting that the popular perception of an all-powerful gene is not on the rise.

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