This Month in the *Journal*

This month in the *Journal,* Heather McDermid and Bernice Morrow (p. 1077) review genetic disorders associated with chromosome 22q11. This region is involved in chromosomal rearrangements that lead to local altered gene dosage. Depending on the dosage, cat-eye syndrome, der(22) syndrome, or velocardiofacial syndrome/DiGeorge syndrome can result. McDermid and Morrow give an overview of these syndromes, discuss the molecular events that cause the 22q11 rearrangements, and outline the candidate genes and mouse models for the disorders.

Haplotype Analysis of the HLA Region, *by Rubio et al. (p. 1125)*

The HLA region has long been known to have an association with susceptibility to multiple sclerosis (MS). However, the high level of linkage disequilibrium (LD) in the region has hampered progress aimed at dissecting the region and pinpointing the variation underlying this association. To get a better handle on the association, Rubio et al. performed a comprehensive analysis, in a case-control study, of haplotypes across the HLA region. Relatives of cases and controls were collected to establish haplotypes that have little ambiguity. A log-linear model was used to look at haplotype interaction in the region and to separate out confounding effects, such as LD. This allowed the authors to determine that the *TNF* locus and other class III genes in the haplotyped class III region are not associated with MS, except by virtue of LD with a class II haplotype. Thus, the class III region has been effectively dissected out of the equation when one is looking at MS susceptibility. They also found further support for previously identified class I and class II MS-susceptibility haplotypes, and these were associated with MS, independent of each other. These haplotypes did not display any higher-order interactions with each other but, instead, had an additive effect. This careful study provides another big step along the road to dissecting the role that the HLA region plays in MS.

Network Analysis of mtDNA Haplogroups, *by Herrnstadt et al. (p. 1152)*

Herrnstadt et al. report on the complete mtDNA coding-region sequences from 560 unrelated individuals from the United States and the United Kingdom. Sequences were analyzed by use of reduced median networks, and, in this report, the authors focused on haplogroup-specific and haplogroup-associated polymorphisms. More than 99% of the sequences could be unambiguously assigned to a single haplogroup, and, in general, the sequences confirm previous haplogroup classifications. In addition, a large number of polymorphisms are reported for the first time, allowing the authors to extend our understanding of the phylogenetic relationships of mtDNA sequences from the major human ethnic groups. There were a relatively large number of sites at which homoplasy, or similarity that is not due to inheritance from a recent common ancestor, occurred. Homoplasy can complicate phylogenetic analysis, especially in small samples, but the authors think that the effects of this homoplasy can be reduced by the use of the additional haplogroup-specific polymorphisms that have been discovered in these sequences. Finally, evaluation of linkage disequilibrium over distance did not reveal any consistent evidence of mtDNA recombination. The mtDNA sequences presented here will be a valuable resource for many types of mtDNA studies.

CNTF *as a Modifier Gene in FALS,* *by Giess et al. (p. 1277)*

Mutations in *SOD-1* are found in ~20% of patients with familial amyotrophic lateral sclerosis (ALS), but the age at onset and the duration of disease can be quite different, even within the same family. The basis for some of this phenotypic variation may be more clear now that Giess et al. report a mutation that influences the age at onset of familial ALS. They describe a patient who died from ALS at age 25 years, after a rapid disease course. He possessed both a missense mutation in *SOD-1* and a homozygous truncating mutation in *CNTF.* Other *SOD-1*–mutation carriers in the family did not carry the *CNTF* mutation in a homozygous state and had either much later disease onset or no symptoms at the time of the study (i.e., at age 35 years). Further supporting the role of *CNTF* as a modifier of ALS onset is the fact that, in sporadic cases of ALS, patients who are homozygous for the *CNTF* mutation have a significantly earlier age at onset than do patients with two intact *CNTF* alleles. The same is true in a mouse model: mice carrying both a *SOD-1* mutation and a homozygous *CNTF* mutation have both an earlier onset of disease and higher rates of motoneuron loss in the lumbar spinal cord than do mice that have the *SOD-1* mutation but that are wild type for *CNTF. CNTF* encodes ciliary neurotrophic factor, which is a survival factor for motoneurons. CNTF does not appear to be essential for motoneuron survival during development, but it is essential for maintenance of function in these neurons postnatally. It has been pro-

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posed that CNTF acts in response to neuron injury or stress, and this may be a possible explanation for its modifying effect on *SOD-1* mutations, which lead to motoneuron cell death.

RNASEL *in Finland,* *by Rökman et al. (p. 1299)*

Recent work by Carpten et al. (see the reference cited by Rökman et al.) suggested that the *RNASEL* gene might be the relevant gene at *HPC1,* a locus for hereditary prostate cancer, on chromosome 1q24-q25. Rökman et al. provide the first confirmation of this association in an independent population, a sample of Finnish families with hereditary prostate cancer (HPC). Seven variants in *RNASEL* were identified in this sample, including the E265X mutation, which was found in an affected family in the study by Carpten et al. E265X was present at a higher frequency in the Finnish families with HPC than in a control sample of blood donors. This difference was particularly apparent if only families with four or more affected individuals were considered and is especially striking because the sample was not selected for linkage to the *HPC1* locus. Not all affected individuals in E265X-positive families carried the mutation, but the median age at diagnosis for mutation carriers tended to be earlier than that of affected individuals who did not carry the mutation. An association was not found between the *RNASEL* variants and unselected cases of either prostate cancer or benign prostatic hyperplasia, so, at least in this sample, *RNASEL* does not appear, at the population level, to have an impact on prostate cancer. The authors speculate that *RNASEL* variants may not be sufficient to cause disease but that, instead, they may act as modifiers of disease onset in HPC. *RNASEL* encodes an RNase that functions in the antiviral and antiproliferative roles of the interferons, and mice lacking RNase L show suppression of apoptosis in thymocytes and fibroblasts treated with apoptotic agents (as described in 1997 by Zhou et al., in an article published in *The EMBO Journal* [vol. 16, pp. 6355–6363]).

***Identification of Human* PKHD1,** *by Onuchic et al. (p. 1305)*

Onuchic et al. report the identification of *PKHD1,* the gene responsible for autosomal recessive polycystic kidney disease (ARPKD), a severe and clinically variable disease that generally presents with enlarged, polycystic kidneys, pulmonary hypoplasia, and liver involvement. This group previously had mapped *PKHD1* to an 834-kb interval on chromosome 6p. In the study reported here, they assembled a transcript map of this interval and targeted, for mutation analysis, transcripts with evidence of kidney expression. In a large gene with complex splicing patterns, they report mutations on 21 of 50 ARPKD chromosomes. Northern blots for the *PKHD1* transcript show the highest level of expression in the kidney, and, consistent with the predicted complexity of alternative splicing in this gene, the transcript appears as a smear rather than as discrete bands. Missense and frameshift mutations are spread across the largest open reading frame in *PKHD1,* which is predicted to encode an integral membrane protein that the authors have dubbed "polyductin." Segments of polyductin share homology with other known proteins and domains, but its function is not yet known. Other splice variants of *PKHD1* potentially could encode secreted forms of polyductin, but it is not known which transcripts are actually translated. *PKHD1* has also been identified recently by Ward et al., in an article in *Nature Genetics* (vol. 30, pp. 259–269 [2002]). An identical gene product was predicted in that article, although it was termed "fibrocystin."

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