This Month in the *Journal*

This month, the *Journal* presents invited editorials that discuss the implications of each of three newly discovered mutations. In the first editorial, Lynn Hudson highlights the findings by Hodes et al. (p. 14), who have discovered unusual duplications of an X-chromosomal region. The duplicated copies, which include the gene encoding proteolipid protein and lead to Pelizaeus-Merzbacher disease, are located distant to the original copy of the region. Next, Zsolt Urbán and Charles Boyd outline the types of elastin-fiber pathologies and discuss how Hinek and colleagues (p. 23) have identified transport defects that disrupt elastic-fiber assembly. Third, James Lupski describes research by Mersiyanova et al. (p. 37) defining mutations in the neurofilament-light gene that lead to Charcot-Marie-Tooth disease type 2. Current models of the pathology of demyelinating neuropathies are discussed.

The connection between a genotype and a phenotype is not always clear-cut, as is the case with the fragile X premutation and premature ovarian failure (POF). In our final editorial, Stephanie Sherman discusses three studies that have been aimed at elucidating this connection. Murray et al. (p. 253) and Vianna-Morgante and Costa (p. 254) have reexamined their data on POF, in response to a recent article by Hundscheid et al. (66: 413–418), which had suggested a parent-of-origin effect for this disorder. Unfortunately, neither of these groups has been able to demonstrate a similar correlation between paternally inherited fragile X premutations and POF in their study populations. Sherman discusses the complexities of this field in the context of these three studies and suggests that further studies must be performed before the relationship between fragile X premutations and POF is resolved.

Identification of the* HMSNL *Gene, *by Kalaydjieva et al.* **(*p. 47*)**

Hereditary motor and sensory neuropathy–Lom (HMSNL) is an autosomal recessive form of Charcot-Marie-Tooth disease that occurs in Romani groups descended from a common founder population. Kalaydjieva et al. have collected a large sample of affected families from several European countries and have used haplotype analysis to narrow down the causative locus for this disorder. They have identified mutations in a gene within this region—*N-myc downstream-regulated gene 1* (*NDRG1*). All of the affected individuals in the sample possessed the same mutation, an R148X truncating mutation. Furthermore, 6 of 10 additional families with unspecified autosomal recessive peripheral neuropathies were found to have the R148X mutation in *NDRG1*. Data in other systems have suggested that *NDRG1* plays a role in growth arrest and cell differentiation during development, and the authors postulate that, in the peripheral nervous system, this gene might be important for both Schwann-cell differentiation and the signaling necessary for axonal survival. This fits with current models of Charcot-Marie-Tooth disease, as outlined in the editorial by Jim Lupski (p. 8).

p63 *Mutations Cause SHFM,* *by Ianakiev et al.* **(*p. 59*)**

The apical ectodermal ridge (AER) is a critical signaling center in the developing limbs of tetrapods. This ridge is crucial for the development of the thumb-pinky axis, proper differentiation of cells in the developing limb, and linear growth of the limb. Studies in mice have demonstrated that p63 is required for the development and maintenance of the AER, with homozygous *p63* mutations leading to defects in limb, craniofacial, and epithelial development. These findings led to the discovery that mutations in *p63* in humans give rise to EEC (ectrodactyly, ectodermal dysplasia, and facial cleft) syndrome (see the 1999 article by Celli et al. that is cited by Ianakiev et al.), a disorder with phenotypic manifestations similar to those seen in *p63*-deficient mice. Split-hand/split-foot malformation (SHFM) shares many of the distal-limb abnormalities that are seen with EEC, including median clefts of the hands and feet, absent or stunted phalanges/metacarpals/metatarsals, and fusion of digits. Ianakiev et al. present two families affected by SHFM and two families affected by EEC. Mutations in *p63* are found in all four families, indicating that SHFM and EEC are allelic disorders. Ianakiev et al. compare the distribution of mutations leading to these two disorders and suggest that the location of the mutation in the p63 protein determines whether it will lead to SHFM or EEC.

Genetic Regulation of Type 1 Diabetes, *by Fox et al.* **(*p. 67*)**

Teasing apart the relationship between genetic loci and phenotypes in complex, polygenic diseases can be a complicated business. Not only are different individuals likely to have mutations at different genetic loci, but each individual may need to have mutations or polymorphisms at more than one locus before the phenotype is seen. To facilitate genetic studies of such a complex dis-

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order—insulin-dependent diabetes mellitus—Fox et al. have used the mouse nonobese diabetes (NOD) model to examine the genetic correlates of one highly penetrant step in the development of diabetes: T cell–dependent progression to a destructive insulitis. Through linkage analysis of the F_2 progeny of NOD mice and the NOD derivative strain NOR (i.e., NOD resistant), the authors have been able to study the effects that various *Idd* loci have on this step in diabetes pathogenesis and have identified an interaction between NOD alleles at the *Idd5* and *Idd13* loci that appears to contribute to T cell–dependent insulitis. The human chromosomal regions orthologous to *Idd5* and *Idd13* also show evidence of linkage to diabetes risk, suggesting conservation of the proteins involved in diabetes pathogenesis. These results show that genetic analysis of simple phenotypes may prove fruitful when analysis of a complex phenotype does not provide conclusive results.

Prostate Cancer Locus on Chromosome 20, *by Berry et al.* (*p. 82*)*;* ***Prostate Cancer–Aggressiveness Loci,*** *by Witte et al.* (*p. 92*)*; and* ***Genomic Scan of Families with Prostate Cancer,*** *by Gibbs et al.* (*p. 100*)

Three articles on prostate cancer illustrate how difficult it is to identify the genetic loci involved in a complex disease. Two of these articles, that by Berry et al. and that by Gibbs et al., identify prostate cancer–susceptibility loci through genome scans. Berry et al. explore the evidence for a locus on chromosome 20q13, whereas Gibbs et al. find putative loci on chromosomes 1, 8, 10–12, 14, and 16, with different results, depending on the model and stratification that are used. Rather than susceptibility loci, Witte et al. search for prostate cancer–aggressiveness loci, using the Gleason score as a quantitative trait. Their data suggest the presence of aggressiveness loci at chromosomes 5q, 7q, and 19q. Differences in sample ascertainment, analysis, and sample stratification exist between the studies, so it is not surprising that overlapping regions were not identified among these studies. This lack of replication of results in the field of prostate cancer genetics in general is disheartening. However, advances are being made in understanding how sample stratification according to age at diagnosis, the presence of male-to-male transmission, and the number of affected family members affect these scans. As more information is gained from studies such as these, it will be possible to reduce the locus heterogeneity in study samples, which will likely increase the replication of results.

Data Mining in LD Mapping, *by Toivonen et al.* (*p. 133*)

Haplotype pattern mining, a new nonparametric method developed by Toivonen and colleagues for linkage-disequilibrium mapping, uses algorithms to sift through input haplotypes to identify repeated patterns. It is based on the idea that individuals affected with a genetic disorder are likely to have higher frequencies of associated marker alleles near the disease gene than are control individuals. The algorithms are used to identify marker-allele haplotypes that occur more frequently on chromosomes containing the disease allele than on control chromosomes. Not only can this method search multiple regions at a time, but test analyses of simulated and real data have proved it to have several additional benefits over other linkage-disequilibrium methods. These benefits include its robustness to missing and erroneous data, the ability to detect disease loci in the presence of high proportions of phenocopies, and the fact that this method does not use model assumptions. The identification of a disease locus for type I diabetes within a region of strong background linkage disequilibrium illustrates the utility of haplotype-pattern mining in deciphering the genetics of complex disease.

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