This Month in the *Journal*

This month we present two review articles related to the genetics of resistance to pathogens. Brownstein (p. 211) discusses variability, in humans and among different inbred mouse strains, in susceptibility to viruses. He considers both the celebrated recent example of a chemokine receptor polymorphism that protects from HIV infection and also some more subtle, but possibly more representative, examples of polymorphisms that influence the progression of viral disease. Poland (p. 215) focuses on resistance to measles. He argues that antiviral antibody-titer following vaccination represents a quantitative phenotype that reflects the host's resistance to active pathogens. Genes that modulate responses to measles-virus vaccination include the major histocompatibility loci and the *TAP* genes, which function in antigen processing.

Multiple Endocrine Neoplasia Type I, *by Bassett et al.* **(***p. 232***)**

Menin is the product of the recently cloned *MEN1* gene, which underlies type I multiple endocrine neoplasia, a multiple-tumor disorder sometimes associated with peptic ulcers. The dominant inheritance and variable clinical course of MEN1 may indicate that menin serves as a tumor suppressor, but its biochemical function has not been demonstrated, and its sequence offers few clues. Bassett et al. have used SSCP and DNA sequencing to identify constitutional *MEN1* mutations in 61 of 63 unrelated MEN1 probands, 57 of whom had family histories of the disease. In all, they identified 47 distinct mutations, all point mutations or short deletions or insertions. The mutations are found throughout the exons and the exon junctions in *MEN1,* and the authors could find no correlation between the type or location of the mutation and the disease phenotype. The number of disease alleles and the frequent occurrence of de novo mutations, often at hot spots with short repeat sequences, suggest that haplotype analysis is of limited use for diagnosis.

Mutation Analysis of Leiomyomatosis, *by Ueki et al.* **(***p. 253***)**

The X-linked form of Alport syndrome (AS), a kidney disease that also presents with eye defects and deafness, results from mutations in the *COL4A5* gene, encoding one of the basement-membrane collagen chains. When deletions in *COL4A5* extend into the neighboring collagen gene *COL4A6,* AS may be accompanied by diffuse leiomyomatosis (DL), a smooth-muscle tumor that characteristically affects the esophagus. Curiously, larger genetic lesions that completely eliminate both collagen genes present only with AS. A critical region of *COL4A6,* including some of its third intron, needs to be spared for DL to occur. It has been proposed that this intron contains structural or regulatory elements of a third, as yet unidentified, gene that represses DL; alternatively, a truncated form of *COL4A6* might affect smooth-muscle-cell growth directly. Ueki et al. now report the sequence flanking the *COL4A6* breakpoint in a man with AS and DL, a first step toward resolving this question. They find multiple consensus sequences for topoisomerases surrounding the breakpoints. This may suggest a mechanism for somatic deletion in the *COL4A5/ COL4A6* region, but the reason for phenotype differences between short and long *COL4A6* deletions remains mysterious.

Pathogenic Mutation in Human Complex I, *by van den Heuvel et al.* **(***p. 262***)**

Respiratory electron-transport chains create the proton gradients needed for oxidative phosphorylation, and defects in the electron carriers in this process can lead to mitochondrial dysfunction and fatal encephalomyopathies. Electron-transport complexes are large multicomponent assemblies. Complex I contains the products of at least 42 genes, most of which are nuclear; defects in complex I function are readily identified at the biochemical level, but genetic analysis has been lacking. van den Heuvel et al. have undertaken to find the causal mutations in a set of 20 complex I–deficient individuals. They used homology to a known bovine sequence to identify a human cDNA for the AQDQ subunit of complex I, which they report here. One of the 20 individuals is homozygous for a 5-bp insertion that shifts the reading frame and extends the C-terminus of the AQDQ protein.

Stop Codons of NF1 as Splice Effectors, *by Hoffmeyer et al.* **(***p. 269***)**

Nuclear-scanning mechanisms have been invoked to explain the sensitivity of intranuclear pre-mRNA splicing and degradation to breaks in the reading frame of nascent mRNA. Although appealing on teleological grounds, and apparently supported in the case of fibrillin mRNA splicing, nuclear scanning remains controversial because there is no obvious mechanism for sensing premature-termination codons (PTCs) in the nucleus. Several groups, including, now, Hoffmeyer et al., have

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sought alternative explanations for the skipping of exons that contain PTCs. Working with RNA from cells from people with type I neurofibromatosis, Hoffmeyer and colleagues show that the processing of neurofibromin mRNA does not respond simply to the presence of PTCs in an internal exon. In sets of alleles with mutations in exon 7 or exon 37 of the 61-exon *NF1* gene, they find that neighboring PTCs may have different effects on mRNA splicing or stability. They further argue that predicted changes in RNA secondary structure, which may introduce, remove, or destroy sequences that participate in splicing, can account for the observed effects of PTCs in this mRNA species.

Methylation Analysis in the DMPK Gene, *by Steinbach et al.* **(***p. 278***)**

Methylation of DNA in CpG islands, noncoding regions enriched for CpG dinucleotides, is associated with changes in chromatin structure and transcriptional activity. Here, Steinbach and coworkers describe a correlation between a trinucleotide-repeat expansion in disease alleles of the myotonic dystrophy (DM) gene, *DMPK,* and the complete methylation of CpG sites within 1.5 kb of the trinucleotide repeat. This hypermethylation is found in cases of congenital DM but not in later-onset cases or in unaffected individuals. Binding of transcription factor Sp1 to a site near the repeat is also inhibited, suggesting that with hypermethylation comes a compact chromatin structure and reduced *DMPK* expression. These observations are consistent with other reports of effects of repeat expansion on local methylation, but they do not readily account for the dominant effects observed for the DM disease allele.

CYP1B1 Mutations in GLC3A, *by Bejjani et al.* **(***p. 325***)**

Here, Bejjani et al. report novel missense mutations in the cytochrome P450 gene, *CYP1B1,* that lead to primary congenital glaucoma. The association of *CYP1B1* with this condition was recently reported in some Turkish glaucoma families. In the Saudi group studied by Bejjani et al., the genetic basis of the disease appears to be simpler. All affected individuals in 25 families were either compound heterozygotes or homozygotes for one of three missense mutations. These findings may be useful for structure/function analysis, as well as for genetic counseling in the Saudi population. The connection between these mutations and PCG, however, remains unclear; Bejjani and colleagues speculate that CYP1B1 may help degrade endogenous growth or differentiation factors during ocular development.

Susceptibility to Relapsing-Progressive MS, *by Hockertz et al.* **(***p. 373***)**

Statistical analysis of human patients and experimental work in animals indicate a role for T cell–receptor (TCR) genes and class II MHC genes in multiple sclerosis (MS). These candidate loci are plausible, because MS is a demyelination disorder that probably develops from autoimmune reactions. Nevertheless, detailed analysis has proved difficult, in part because of complex allele-specific interactions between these loci. Hockertz and coworkers argue here that two factors—the failure to distinguish among clinical forms of the disease and the improper choice of control populations—have led researchers to contradictory conclusions. Here, they employ family-based controls and stratify their group for patterns of disease progression. They find that two distinct genotypes, consisting of different haplotypes at the TCR locus and a polymorphism at the HLA-DR locus, are significantly associated with the relapsing-progressive—but not with the relapsing-remitting—form of the disease.

mtDNA in Aboriginal Australians, *by van Holst Pellekaan et al.* **(***p. 435***)**

mtDNA sequence divergence provides the basis for much of the genetic reconstruction of human migrations, but this technique has not been applied extensively to Australian aboriginal peoples. van Holst Pellekaan et al. have acquired DNA samples from two culturally and linguistically distinct groups, one from the north-central "desert" region and one from the "riverine" region of southeastern Australia. They also developed a novel metric for mtDNA sequence divergence, BEPPI, the between-population proportion index. This statistic describes the relation between the number of sequence differences in a sample and the proportion of all sequence pairings that compare DNAs from different groups. They find distinct distributions of mtDNA sequence types between the desert and riverine peoples, consistent with their assumed isolation. Comparisons with outside groups show that the aboriginal populations are most closely related to each other and that they are genetically nearer to New Guinea highlanders than to other Pacific or African peoples. This reconstruction is consistent with anthropological and genetic evidence suggesting a common founder population for the present-day Australian aborigines and New Guinea highlanders.

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