This Month in the *Journal*

This month we present a series of articles on the genetics of immune systems. Ober (p. 1) discusses the immunogenetics of pregnancy. She focuses on the issue of maternal-fetal immune tolerance and on the HLA-G protein, a relative of the class I major histocompatibility antigens that is expressed in placental tissue. Ezekowitz (p. 6) reviews the roles of the mannan-binding protein, the best characterized of the so-called pattern-recognition receptors. These are mediators of immune activation that do not depend on immunological memory or on clonal expansion of specific immune-cell lineages. Pattern-recognition receptors, which may have participated in the earliest forms of host defense, are thought to bind to structural features that are conserved pathogens and to provide antimicrobial defense during the initial stages of infection, while the clonal immune system is being activated. Similarly, Dushay and Eldon (p. 10), writing in the series "Insights from Model Systems," discuss the fruit fly's nonclonal immune system, which displays a surprising degree of specificity in its response to different pathogens. As Dushay and Eldon explain, the study of fly immunity has already brought to light conserved mechanisms of immune activation that also operate in human clonal responses.

Mitochondrial A1555G Mutation and Deafness, *by Estivill et al.* (*p. 27*)

The mtDNA point mutation A1555G occurs in the gene for the mitochondrial 12S rRNA. This mutation leads to sensitivity to the cytotoxic effects of aminoglycoside antibiotics, presumably by rendering the mitochondrial ribosome subject to inhibition by the drug, just as these compounds inhibit translation in prokaryotes. Antibiotic toxicity is observed specifically in cochlear cells, and numerous families have been reported in which the A1555G genotype, combined with exposure to streptomycin or to other aminoglycosides, led consistently to sensorineural deafness. The report of Estivill and colleagues suggests, however, that the prevalence of this problem has been underestimated. Among 70 Spanish families in which at least 2 members exhibit nonsyndromic deafness, the authors noted 19 with matrilineal inheritance of the condition; all 19 proved to carry the A1555G mutation, whereas control populations were free of it. mtDNA haplotype analysis showed that the mutation occurred on several highly divergent backgrounds, confirming that this mutation is causal. While the requirement for the A1555G mutation in maternally inherited deafness thus appears to be absolute, the role of antibiotics is less clear. Indeed, aminoglycoside treatment preceded onset of deafness in only a minority of cases, and 16 of the 19 families had at least one deaf member who had not been exposed to these drugs.

Sanfilippo Syndrome Type B, *by Zhao et al.* (*p. 53*), *and* ***Sanfilippo B Mutations,*** *by Schmidtchen et al.* (*p. 64*)

The recessive lysosomal-storage disease Sanfilippo syndrome type B is caused by a lack of α-N-acetylglucosaminidase (NAGLU), leading to accumulation of heparan sulfate in the tissues and to a slowly progressing, but ultimately fatal, cerebral atrophy. Now, two groups report a series of mutant *NAGLU* alleles from independently ascertained individuals. Zhao et al. identified eight novel mutations in *NAGLU*, as well as six novel polymorphisms. In their study, one affected individual, a compound heterozygote who carries an in-frame insertion and a conservative missense mutation, was unusual in that she is only mildly mentally retarded, suggesting that one or both of these alleles retains some enzymatic function. Another unusual genotype was found in an unaffected person with low levels of plasma NAGLU, who carries two different silent mutations in the coding region of the gene. Because these alterations would require the use of nonoptimal codons, they might compromise NAGLU translation, an effect that is well documented in microbial systems but not in humans. Schmidtchen et al. also identified 10 novel mutations, including 6 missense mutations that they showed to be nonfunctional when expressed in cultured cells. Only one mutant allele was found in common between the two studies, indicating a high degree of heterogeneity in Sanfilippo syndrome.

PS-1 ***Mutations in Early-Onset Alzheimer Disease,*** *by Tysoe et al.* (*p. 70*)

The presenilin-1 gene (*PS-1*) has been associated with early-onset Alzheimer disease (EOAD), in family studies, but its relevance to the sporadic form of AD has not been clear. Tysoe and coworkers have screened for PS-1 mutations in tissues from 40 autopsy-confirmed EOAD individuals who were not preselected for familial occurrence of the disease. They found only one mutation, which was shared by two apparently unrelated people in this group. This mutation, a novel point mutation in a splice consensus sequence, leads to aberrant splicing of the PS-1 mRNA and to the generation of two trun-

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cated and frame-shifted open reading frames. Tysoe et al. argue that these transcripts do not encode functional PS-1 protein, suggesting that haploinsufficiency for *PS-1* predisposes to AD. If so, a second event, such as loss of heterozygosity at this locus, may be required for onset of disease.

Analysis of the* COL1A1 *and* COL1A2 *Genes, *by Körkkö et al.* (*p. 98*)

Although hundreds of disease alleles have been identified in the interstitial collagen genes *COL1A1* and *COL1A2,* no systematic approach has been available to search for such mutations in people with osteogenesis imperfecta (OI). This has been a particular problem in cases of mild, or type I, OI, in which null alleles, rather than dominantly acting alleles, are the rule. Such null alleles often carry premature-termination codons and, hence, encode unstable mRNAs, which makes it difficult to observe the mutations at the RNA or protein levels. By sequencing a total of 50 kb from these two genes and by developing PCR primers that allow them to perform heteroduplex analysis, Körkkö et al. have made it possible to find sequence alterations in any of the exons of these collagen genes. Using this technique, the authors have identified polymorphisms in both genes, as well as probable disease alleles in each of 15 unrelated people with type I OI. No mutations were found in *COL1A2,* possibly reflecting some bias in ascertainment. The authors also speculate that specific mutation-prone sequences found in *COL1A1,* but not in *COL1A2,* might account for this discrepancy.

Deficient Transcription in Friedreich Ataxia, *by Bidichandani et al.* (*p. 111*)

Friedreich ataxia is an unusual autosomal recessive neuropathology that arises from expansion of an intronic GAA repeat sequence in the gene that encodes frataxin, *X25*. Early onset of the disease correlates with long GAA tracts in the shorter of the two alleles, which is consistent with a dampening of frataxin expression in longer *X25* alleles. Bidichandani and colleagues now provide tantalizing clues to the molecular basis of this effect. PCR-amplified fragments of the intron from *X25* are readily transcribed in vitro when they include short GAA tracts, but, as repeat length increases into the range associated with disease alleles, transcription by either bacteriophage or human RNA polymerase is blocked. Equal-sized inverted sequences (containing TTC repeats on the transcribed strand) create no such blockage. The structure of the repeat-containing DNA is also unusual, as assessed by sensitivity of the amplified sequence to chemical agents that fail to cleave normal B-DNA, under physiological conditions. The connection between these observations remains tentative, but, as the authors suggest, the effect of the orientation of the tract could be explained if the nascent transcript forms a complex with the transcribed DNA.

Mapping of the Athabascan SCID Gene, *by Li et al.* (*p. 136*)

Native American speakers of the Athabascan family of languages, including the Apache and the Navajo peoples, are now widely spread throughout North America. They originated in the Northwest Territories ~700 years ago, where another Athabascan-speaking group, the Diné, still resides. In each of these groups are found infants with a severe autosomal dominant form of immunodeficiency that affects both B- and T-cell lineages. Having worked with 14 affected families from these three tribes, Li et al. now report linkage of the Athabascan severe combined immunodeficiency (A-SCID) locus to a 6.5-cM region on 10p. The disease phenotype is similar to that seen in recombination-activating gene (RAG) deficient or SCID animals, which fail to rearrange the DNA at immunoglobulin and T-cell receptor loci. However, all genes known to function in the rearrangement pathway are excluded by this chromosomal assignment.

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