This Month in the *Journal*

Gene therapy is the topic of this month's "Human Genetics '97" series. Hall et al. (p. 785) discuss one of the major challenges in cancer gene therapy, the need to suppress the growth of even those tumor cells that fail to take up or express a transgene. Kozarsky and Couture (p. 790) describe a variety of therapeutic strategies that affect mRNAs directly, rather than targeting DNA sequences. In "Insights from Model Systems," Hendrickson reviews DNA double-strand-break repair pathways. Many of the molecules involved are conserved between mammalian and yeast cells and have been implicated in hereditary cancer or immunodeficiency disorders.

Renal Cysts in Tuberous Sclerosis, *by Sampson et al. (p. 843)*

The *TSC2* gene underlies many cases of tuberous sclerosis, which presents with hamartomas, often on the skin or in nervous tissue. Renal symptoms include angiomyolipomas and, in some patients, kidney cysts. Here, Sampson and colleagues describe genomic deletions in people with both tuberous sclerosis and kidney cysts. They show that, in 18 of 27 unrelated subjects, constitutive deletions in *TSC2* also affected the tightly linked *PKD1* gene, a major gene involved in autosomal dominant polycystic kidney disease. Thus, tuberous sclerosis with kidney cysts appears to be a contiguous gene–deletion syndrome. Consistent with this model, Sampson et al. find that an individual who carries a deletion in *PKD1* that leaves the coding region intact shows only mild cystic disease, and they find that somatic mosaicism for deletions in the two genes leads to cystic disease with variable severity.

Fructose-1,6-Bisphosphatase Deficiency, *by Kikawa et al. (p. 852)*

Fructose-1,6-bisphosphatase is a key regulator of gluconeogenesis, and deficiency of this enzyme leads to life-threatening metabolic defects in infants. Kikawa et al. have identified three novel and one known disease allele in the *FBP1* gene in a set of 11 unrelated Japanese families. Two of these mutations are missense alterations at conserved sites in the protein sequence. The authors suggest that these four mutations, which abolish enzymatic activity when they are expressed in bacteria, act by blocking the effects of AMP, an allosteric activator of the enzyme.

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X-Linked Dilated Cardiomyopathies, *by D'Adamo et al. (p. 862); and* ***INVM Is Allelic with Barth Syndrome,*** *by Bleyl et al. (p. 868)*

Taffazins are recently discovered proteins with no known biochemical function that are highly conserved between humans, nematodes, and yeast. In humans, these proteins arise from alternatively spliced mRNAs, the products of a single X-linked gene, *G4.5*. One or more of the taffazins are altered in Barth syndrome (BTHS), a cardiomyopathy that also presents with growth arrest, neutropenia, and defects in skeletal muscle. Now, two groups have implicated *G4.5* in other X-linked infantile cardiomyopathies. D'Adamo et al. report that mutations in *G4.5*, including missense mutations in alternatively spliced exons, may lead to endocardial fibroelastosis or to severe X-linked cardiomyopathy, diseases that had been considered distinct from BTHS. D'Adamo et al. suggest that the clinical differences between BTHS and the other condition occur because the mutations affect different subsets of the taffazins. However, Bleyl et al. report on a Utah kindred with a mutation identical to one of the point mutations found by D'Adamo et al., and in this family the noncardiac symptoms of BTHS present inconsistently. Hence, not all the clinical heterogeneity in these conditions can be ascribed to different mutations in *G4.5*.

Familial Glaucoma Iridogoniodysplasia Maps to 6p25, *by Jordan et al. (p. 882)*

Juvenile-onset glaucoma and a distinctive slate-gray–colored iris are diagnostic criteria for familial glaucoma iridogoniodysplasia (FGI), an autosomal dominant eye disorder. This condition has been studied in a large nine-generation Scots family in which the earliest record of disease dates from the 18th century. Working with a branch of this pedigree, Jordan and co-workers have mapped the FGI locus to a 6.4-cM region on 6p25. Their data show that FGI is distinct from Rieger syndrome but suggest that it may be allelic with primary congenital glaucoma, a recessive disorder, or with iridogoniodysgenesis anomaly.

Linkage of ICCA Syndrome to Human Chromosome 16, *by Szepetowski et al. (p. 889)*

Szepetowski and co-workers have identified families in which two clinically distinct convulsive disorders segregate, apparently as a single autosomal dominant trait. Benign infantile familial convulsions are observed in most affected individuals in these families, within the 1st year of life. Paroxysmal choreoathetosis (CA), on the other hand, is first seen at age 6 years and may exhibit age-dependent penetrance. Szepetowski et al. ex-

clude linkage of infantile convulsions and CA (ICCA) with any of the reported epilepsy-susceptibility loci, but they link ICCA with a novel locus on chromosome 16. The identification of ICCA as a single genetic entity strengthens the argument that CA should be regarded as a type of epilepsy.

Evidence for Eight Fanconi Anemia Genes, *by Joenje et al. (p. 940)*

At the cellular level, Fanconi anemia (FA) is a chromosomal breakage disorder, and FA lymphoblasts are hypersensitive to DNA cross-linking agents. FA is genetically heterogeneous, as shown by the patterns of complementation in cell-fusion studies using cell lines from FA individuals. The chromosomal instability phenotype no doubt leads to the clinical features of FA, such as loss of myeloid cells and susceptibility to leukemia, but the molecular basis of the condition is not understood. Joenje and colleagues have defined three novel complementation groups, bringing the total number of FA loci to eight. To date, only two of these, *FAA* and *FAC,* have been cloned, but characterizing the remaining genes may provide new insights into chromosomal stability or DNA repair.

Predictive Testing for Huntington Disease, *by Almqvist et al. (p. 945)*

Risk assessments that genetic counselors provide their clients are always provisional. If more family data are collected, if diagnostic criteria change, or if genotyping errors are discovered, it may be necessary to contact clients and offer them a revised risk assessment. Almqvist et al. have collected case studies of dramatic reversals in assessed risk for Huntington disease. They report here that clients' responses were complex and not readily predictable, regardless of whether the newer assessment is for greater or lesser risk than was originally stated.

JOHN ASHKENAS
Editorial Fellow