This Month in the *Journal*

This month we introduce "Insights from Model Systems," a new series of editorials in which experts from outside this discipline review their fields and their findings with an eye toward the interests of human geneticists. Typically, these papers will describe work done in model organisms that allow sophisticated genetic analysis. This month, Antic and Keene (p. 273) describe a family of proteins, conserved between flies and humans, that regulate gene expression by controlling the stability of certain mRNAs. The "Human Genetics '97" series continues with two papers that are concerned with other strategies that cells use to alter their pattern of gene expression. Cooper and Mattox (p. 259) discuss alternative splicing and its relation to human disease, and we (p. 267) address protein degradation as a protective response of cells that express abnormal proteins.

KIP2 ***Coding Mutations in Beckwith-Wiedemann Syndrome,*** *by O'Keefe et al. (p. 295); and* ***p57^{KIP2} Mutation in Beckwith-Wiedemann Syndrome,*** *by Lee et al. (p. 304)*

Beckwith-Wiedemann syndrome (BWS) is a disorder of generalized overgrowth in utero. Some BWS infants go on to develop Wilms tumor (WT). BWS has been linked to the imprinted region of 11p15, where the cell-cycle inhibitory gene *KIP2* resides, so *KIP2* has been a promising candidate gene for BWS and/or WT. Consistent with this, WT and BWS constitutional tissues show abnormal patterns of *KIP2* expression. However, two groups now show that alterations in *KIP2,* either genetic or epigenetic, do not account for most cases of these disorders. O'Keefe et al. report that, among five infants with BWS, only one carries an identifiable mutation in the gene; this child was also the only one with a family history of BWS. This mutation, a short in-frame deletion, greatly reduced the growth-suppressive activity of *KIP2* in transfected cells. In WT tissues, loss of heterozygosity in 11p15 does not necessarily affect *KIP2,* suggesting that other linked loci may be involved. Lee et al. confirm that few BWS cases involve constitutional mutations in *KIP2,* and they suggest that another imprinted gene in the same cluster, K_VLQT1, may be involved in some cases.

Mutations in Batten Disease Gene **CLN3,** *by Munroe et al. (p. 310)*

Batten disease, a childhood neurodegenerative condition characterized by the intracellular accumulation of lipofuscin granules in neurons and lymphocytes, arises from mutations in the *CLN3* gene. Munroe et al. report here on their search for novel disease alleles in *CLN3*. In their group of 188 unrelated Batten disease patients from 16 countries, they find 19 novel mutations, of which 5 are found in multiple affected individuals. The most prevalent of the Batten disease alleles is the previously identified 1.02-kb deletion, and virtually all affected people studied carried this allele in at least one copy. Hence, although it is not likely to be practical to screen for all rare or private mutant alleles, the presence of the 1.02-kb deletion in diagnostic evaluations should be sufficient to spur a search for a second mutant allele in a family. Three of the six missense mutations identified may represent less severe or tissue-specific alleles of *CLN3,* because, when present in compound heterozygotes with the 1.02-kb deletion, they appear to spare cognitive function but to be associated with loss of vision.

SCA6 ***Gene in Japanese ADPCA,*** *by Ishikawa et al. (p. 336)*

Trinucleotide repeats in any of several genes can lead to cerebellar ataxia disorders, and this appears to be the case as well for the recently discovered gene *SCA6,* which encodes a voltage-gated calcium channel. In ataxic disease linked to *SCA6,* the onset of symptoms occurs at variable ages, from the mid 20s to the 80s, and the progress of the disease is slow, as monitored by motor symptoms or by cerebellar atrophy. As Ishikawa et al. now show, CAG-repeat length at an exonic site in *SCA6* is inversely related to affected status and, among affected individuals, to age at onset. However, the range of sizes in both affected and unaffected groups is small, and there are no convincing data for anticipation. Average repeat length among healthy Japanese is 13 CAG repeats, with some repeats as long as 20 repeats. Disease alleles may be as short as 21 repeats; the longest, associated with onset in the late 50s, contains only 25 repeats. This association is surprising, in view of the subtle differences in length, and it will be important to validate results by use of larger samples.

Pregnancy-Induced Hypertension and **eNOS** ***Gene,*** *by Arngrímsson et al. (p. 354)*

Arngrímsson et al. report here that pregnancy-related hypertension may be attributed to defects in the gene for endothelial NO synthase (*eNOS*). The authors define the condition, which is highly variable, as the presence of two or more of the signature features of the disorder: pregnancy-induced hypertension, proteinuria, and intrauterine growth retardation. Because NO is a potent vasodilator, and because NO levels normally increase during pregnancy, *eNOS* was an attractive candidate gene. Linkage analysis on women in 50 Icelandic and Scottish

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families confirms that a locus in or near the *eNOS* gene is strongly associated with preeclampsia, data that set the stage for mutational analysis within the *eNOS* gene.

Duplication of Xq28 in BPNH, *by Fink et al. (p. 379)*

Bilateral periventricular nodular heterotopia (BPNH) is a developmental brain disorder that can be diagnosed at the anatomical level by brain imaging. Unusually for an X-linked condition, BPNH is typically observed only in females, who present with epilepsy; affected males generally die in utero, but some boys survive and exhibit symptoms that are more severe than those seen in girls. Fink et al. have studied three of these rare male BPNH individuals, all of whom are mentally retarded and exhibit syndactyly. Guided by a subtle cytological abnormality shared by one of these boys and his mother, the authors performed FISH using probes to distal Xq and defined an inverted repeat over a region $\leq$3.25 Mb at Xq28, where BPHN maps. These findings should greatly simplify the search for the gene(s) involved.

A Gene for Laterality Defects in Xq26.2, *by Ferrero et al. (p. 395)*

As with the anterior-posterior and dorsal-ventral embryonic axes, the left-right axis needs to be established for normal developmental morphogenesis to occur. Situs inversus is a clinically benign condition in which internal organs are uniformly located at the mirror image of their normal locations; situs ambiguus, however, in which left-right distribution is disrupted rather than reversed, is usually lethal. Ferrero and coworkers report here that they have refined the mapping of an X-linked genetic lesion that can cause situs ambiguus. A 19-cM region of Xq had been implicated in familial and sporadic situs inversus, but Ferrero et al. have now narrowed this region by conducting more familial linkage studies and by identifying in one individual with situs ambiguus an ~1-Mb deletion derived from his mother. They argue that both types of situs defects are likely to arise from a lesion in a single gene at Xq26, and they suggest that the identity of this gene will help explain how developmental patterning occurs along the left-right axis.

Plasma Lp(a) in African Americans, *by Mooser et al. (p. 402)*

High plasma levels of Lp(a) represent, at least among Caucasians, a significant risk factor for heart disease. Lp(a) levels vary little with age and do not appear to respond to diet or other environmental effects but do correlate with race: average and median levels among Africans and their African American descendants are two to three times higher than those among Caucasians or Asians. Mooser et al., who previously had investigated the heritability of Lp(a) levels among Caucasians, now report that, in a set of 49 African American families, virtually all intersibling variability can be attributed to a haplotype near the apo(a) locus. The different plasma levels of Lp(a) found in the two groups might be explained if *cis*-acting sequences common to the different African haplotypes confer higher expression levels. The authors argue instead that race-specific differences in Lp(a) biosynthesis, attributable to other genetic differences, underlie the quantitative differences in Lp(a) level.

First-Degree Relatives: LOH and Linkage, *by Rohde et al. (p. 418)*

Loss of heterozygosity (LOH) in known tumor-suppressor genes is commonly studied to help define the mechanisms of tumor development. It is less widely appreciated that LOH data can also be used to help map novel tumor-suppressor genes. Because LOH will preferentially affect markers near a tumor-suppressor gene of interest, and because it should only lead to cancer if it is the wild-type gene that is affected, LOH data from tumors of related patients can provide information on both linkage and phase. Rohde et al. have developed mathematical techniques for this analysis, and they show here that LOH data increase the statistical power of linkage analysis and that it can be used to generate linkage information from affected parent-offspring pairs, which would be uninformative otherwise.

Inference of Relationships in Sib Pairs, *by Boehnke and Cox (p. 423)*

Inaccurate or incomplete information taken in a family history—misidentifying a half-sib as a sib, for example, or failing to note that an individual was adopted—can complicate linkage analysis and reduce the level of confidence in resulting mapping data. Boehnke and Cox now provide a statistical tool to correct such erroneous information prior to the calculation of linkage. The method, which uses the observed degree of sequence to calculate the most likely relationship between two individuals in a pedigree, can determine the actual degree of relatedness by use of even a small number of markers, so long as the markers used are highly polymorphic. Boehnke and Cox used this technique, which they have made available as a computer program, to reexamine a published analysis of linkage in non–insulin-dependent diabetes mellitus (NIDDM). They show that, by excluding data from putative sibships that appear unlikely to be related as described, they achieve a modest increase in confidence in linking NIDDM to the most promising of the loci from the original study. As they point out, if such data were used (not excluded), and if the correct relationship between individuals were specified, still greater increases in statistical power should be possible.

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