This Month in the *Journal*

This month in the *Journal,* Altmüller et al. (p. 936) discuss the difficulties with linkage discovery in genomewide scans of complex disease. They created a database of 101 of these scans, which is almost all of the scans that had been performed as of December 2000, and analyzed the success of this methodology. No single study design is clearly better than another, and the only factors that appear to improve the chance of success in a genomewide scan are an increase in the sample size and an increase the homogeneity of the sample.

The other review this month, by Resendes et al. (p. 923), discusses the many different forms of hereditary deafness and the molecular mechanisms underlying hearing impairment. The genes known to be involved are numerous and still increasing, and this review provides an overview of the nature of these genes and their functions, as well as some insight into the ways that mutations in these genes lead to phenotypes that are sometimes quite variable.

***Identification of Human*TSIX,** *by Migeon et al. (p. 951)*

The transcript from the *Xist* gene in mice initiates the process of X inactivation for the chromosome from which it is transcribed. A second transcript, from the gene *Tsix,* is partly antisense to the *Xist* transcript and is believed to protect the active X from being shut off by *Xist*. Humans also express an *XIST* transcript, but no ortholog to *Tsix* had been identified definitively until Migeon et al. used reverse-transcription–PCR primers spaced across the human X-inactivation center and found only one transcript, in addition to *XIST,* in this region. The gene encoding this transcript is believed to be the human counterpart of *Tsix*. It is an antisense transcript that partially overlaps *XIST,* and it is expressed only in cells of fetal origin. However, *TSIX* is truncated at its 5′ end relative to *Tsix,* it does not overlap the *XIST* promoter, and it lacks the CpG island that is crucial for *Tsix* function. Furthermore, there is coexpression of *TSIX* and *XIST* in embryo-derived cells, indicating that *TSIX* expression does not repress *XIST* expression, as has been proposed to occur in mice. An evolutionary breakpoint appears to have shortened the *TSIX* locus, compared to the mouse locus. These murine/human differences at this locus indicate that the *TSIX*/*Tsix* orthologs may not function in the same manner.

0002-9297/2001/6905-0001$02.00

Oculocutaneous Albinism 4, *by Newton et al. (p. 981)*

Mice that possess certain alleles in the *underwhite* (*uw*) gene show generalized hypopigmentation. On the basis of the phenotype of these mice, the protein encoded by this gene appears to be a major determinant of pigmentation. Other mouse strains with generalized pigmentation defects have mutations in genes whose human orthologs are mutated in people with oculocutaneous albinism (OCA), a generalized pigmentation defect that affects eye development and that leads to an increased risk of skin cancer. This implicates the human ortholog of the *uw* gene in OCA. Newton et al. identified one expressed-sequence tag that was restricted to skin and eye, tissues that contain melanocytes, in the human chromosome 5p region, which is syntenic to the mouse region containing *uw.* This gene, dubbed "*MATP,*" is mutated in one patient with OCA, thereby defining a fourth type of OCA, OCA4. The mutation alters a splice-acceptor sequence and would result in the skipping of exon 2 of *MATP.* A recent article in *Nature Genetics* (see the reference to Fukamachi et al., in Newton et al.'s article) reported mutations of the medaka-fish ortholog of *MATP* in fish with generalized hypopigmentation. Although the role of the proteins encoded by these genes is unclear, homology searches indicate that MATP is a transporter and that it possesses a sucrose-transporter signature sequence.

COL3A1 ***Null Mutations Cause EDS Type IV,*** *by Schwarze et al. (p. 989)*

More than 200 mutations in *COL3A1,* the gene encoding the chains of type III procollagen, have been identified in people with Ehlers-Danlos syndrome type IV (EDS type IV). EDS type IV is a collagen-deficiency syndrome, the most severe complications of which are spontaneous rupture of the bowels and large arteries. These mutations all lead to the synthesis of abnormal type III procollagen. It has been speculated that *COL3A1* haploinsufficiency may lead to a less severe phenotype than is seen with mutations that produce abnormal collagen chains. Schwarze et al. examined cells from individuals with possible and probable EDS type IV, looking for the presence of *COL3A1* mRNA from both alleles. Three patients showed stable transcript from only one *COL3A1* allele, owing to premature truncating codons in the other allele, whereas one patient possessed a nonsense mutation, near the end of the gene, that did not affect transcript stability. The defective procollagen chains produced from the stable mutated transcript persisted as monomers in the cells of the

patient and therefore did not appear to be incorporated into collagen trimers. All four mutations in this study therefore result in protein deficiency, yet the phenotype associated with these mutations does not differ from that produced by mutations that lead to abnormal type III procollagen.

Excess Twin Pairs in Autism, *by Greenberg et al.* (*p. 1062*)

The factors, other than genetics, that influence the development of autism are unclear. To examine twinning as a potential risk factor for autism, Greenberg et al. collected a sample, through the Autism Genetic Resource Exchange, of families with exactly two autistic offspring. The observed twinning rates in this sample were substantially different than those predicted by population twinning rates. For this difference to be attributable to an ascertainment bias, the authors calculate that autistic twin pairs would have to be 11.9 times more likely than nontwin affected sib pairs to be ascertained in the study. A sample of diabetic families that was collected in a similar manner did not show a significant deviation from the expected amount of overall twinning, suggesting that the method of sample ascertainment does not inherently result in a sample with a high number of twins. The fact that there is an excess of MZ twins in the autism sample supports a genetic basis for autism, but the excess of MZ and DZ twins in the sample suggests that risk factors related to twinning itself may contribute to autism.

Mutation Rates in the mtDNA CR, *by Heyer et al.* (*p. 1113*)

mtDNA mutation-rate estimates derived from large pedigrees are much greater than those estimated from phylogenetic data. Heyer et al. attack this discrepancy, using control-region sequence in deep-rooting pedigrees from Quebec. To increase the number of transmissions examined, they combine these data with those from pedigrees in other studies. In addition, unrelated European control-region sequences were gleaned, from a database, to use in phylogenetic calculations of mutation rates. Heyer et al. find that mutation-rate heterogeneity in the control region can be defined by three classes of sequence sites: those with slow, moderate, and fast mutation rates. Sites with a fast mutation rate make up a minority of the sites, but they are preferentially identified in pedigree studies; on the other hand, sites that rarely show substitutions are more likely to be found in phylogenetic studies. This work begins to reconcile the differences, in mutation-rate estimates, between pedigree and phylogenetic studies, and additional data in this area should make it possible to more accurately calibrate the molecular clock of mtDNA mutation rates.

KATHRYN BEAUREGARD
Deputy Editor