# This Month in the Journal

We focus this month on statistical issues in human genetics, with four articles on a variety of mathematical tools for the identification and mapping of genetic loci. Elston (p. 931) reviews the relative merits of various model-free and model-based linkage methods, and he ends with a discussion of the significance levels in whole-genome screens. Schaid (p. 935) discusses the development of the haplotype relative risk and the transmission-disequilibrium tests. He points out various pitfalls in the application of these and related model-free methods. Jarvik (p. 942) discusses complex segregation studies, which, she argues, serve as a valuable first step that should be taken before one embarks on linkage analysis of complex genetic traits; she considers the potential power of this approach, as assessed in simulation studies, and she also examines its record in real applications to human disease, such as in the identification of the mode of transmission of genes that underlie prostate cancer or breast cancer. Finally, Vieland (p. 947) argues that a Bayesian approach to linkage analysis is superior, both practically and in terms of logical consistency, to conventional analyses, which focus on type I error rates. She finds that metanalysis among independent linkage studies could be simplified by use of the posterior probability of linkage (as calculated from Bayes theorem), rather than the *P* value of a finding.

Also in this issue, Walhout et al. (p. 955) discuss the growing importance of the nematode *Caenorhabditis elegans* as a model for the study of the development and physiology of larger animals such as ourselves. With this worm's compact genome now almost fully sequenced, it has become practical to examine, in a comprehensive and systematic fashion, all the possible interactions among the proteins that it encodes and to provide this information freely to the community of researchers.

***Congenital Myasthenic Syndrome,*** *by Donger et al.* **(***p. 967***)**

Congenital myasthenia syndromes (CMS) may arise from the loss of acetylcholine receptor function at the neuromuscular junction (NMJ), because of defects in the genes for either acetylcholinesterase (AchE) or subunits of the acetylcholine receptor. In the type Ic form of CMS, NMJs are abnormal, with small muscle end plates that contain little or no AChE. Expression of AChE on this structure of the muscle cell is sensitive to collagenase, and a unique collagen species, collagen Q, is known to associate with AChE; this interaction may be lost in some families with CMS-Ic. Donger et al. have now cloned the human collagen Q cDNA, and they have found a missense mutation in *COLQ,* which segregates with a mild form of CMS-Ic in one family. Curiously, this mutation does not interfere with interactions between AChE and collagen Q, but it seems to prevent the localization of the complex to the muscle end plate.

**Hairless *Gene Mutation in Congenital Atrichia,*** *by Ahmad et al.* **(***p. 984***)**

Hair growth in normal mammals is limited by the duration of anagen, the active phase of the hair cycle, during which time hair-follicle matrix cells proliferate and differentiate into the hair root and shaft cells. In people with congenital atrichia, a single hair cycle proceeds normally, with the expected shedding of the natal hair, but the growth fails to resume during the first adult hair cycle. A similar pattern is seen in mice with homozygous loss-of-function alleles in the *Hairless* gene, which encodes a zinc-finger–family transcription factor. One mutation in the human homologue, *HAIRLESS,* has been identified in a family with autosomal recessive loss of hair. In that family and in a second family that Ahmad and colleagues now report, the complete loss of head and body hair is accompanied by the degeneration of hair follicles and the growth of cysts in their place. These findings and a similar phenotype in the mouse mutant implicate the Hairless protein in transcriptional regulation of follicle and epidermal cell growth and differentiation.

***CpG-Methylation Levels in Human Germ Cells,*** *by El-Maari et al.* **(***p. 1001***)**

Methylated cytosines, which occur preferentially in CpG-rich sequences, are prone to mutations, but it has not been clear whether this methylation represents a rate-limiting event in the appearance of mutations in human genes. Here, El-Maari and co-workers show that levels of methylation at specific CpG dinucleotides are poor predictors of mutation rates in oocytes and spermatocytes. The authors have examined the methylation pattern in two genes that are subject to frequent mutation, in DNA from isolated germ cells. They find no differences that could account for the strong bias for paternal, rather than maternal, de novo mutations. In fact, most sites were heavily methylated in both cell types, and even relatively infrequently methylated sites can appear as hot spots for mutation. Differences in the rate of mutation may be found, as the authors suggest,


0002-9297/98/6304-0001$02.00

in the large number of cell divisions that occur in spermatogenesis during a man's lifetime, relative to the fixed—and smaller—number of divisions in oogenesis; different rates of mismatch repair might provide an alternative explanation.

**SNRPN *in Human Preimplantation Embryos,*** *by Huntriss et al.* **(*p. 1009*)**

Huntriss et al. have taken advantage of a common polymorphism in the *SNRPN* gene to follow the temporal pattern of expression of this maternally imprinted gene before and shortly after conception. Eggs donated by women who are heterozygous for this polymorphism carry SNRPN mRNA derived from both alleles, confirming that the imprint has been erased during oogenesis. These mRNA species are unstable after fertilization, however, and by the 4-cell zygote stage, material derived from the oocyte is undetectable by reverse transcription–PCR. When such early preimplantation embryos are generated in vitro from the gametes of "informative" couples (in which parents are both homozygous, each for a different allele), only the paternally derived allele is expressed. This early developmental imprinting has also been observed in mice, a species that seems to be a reliable model of human imprinting.

***Phenotypic Variation in VHL Disease,*** *by Webster et al.* **(*p. 1025*)**

von Hippel–Lindau (VHL) disease presents with a variety of tumor types, in the nervous system and the kidney and elsewhere. The *VHL* defect, which underlies this familial cancer syndrome, is inherited as a dominant loss-of-function allele; tumor growth requires a second, somatic event, which may be epigenetic, rather than genetic. The course of the disease is highly variable among people hemizygous for a functional *VHL* allele, but phenotypic similarities within families raise the question of whether modifier genes affect VHL's presentation or progression. Webster et al. now address this possibility by comparing the occurrence of ocular angiomas—a benign tumor type that is easily studied by gonioscopy, without the need for invasive procedures—in VHL kindreds. All affected members in a single family are expected to carry an identical mutant allele, and Webster et al. find significant correlation in the number of angiomas within either parent-child pairs or pairs of siblings. However, these correlations are not significant among more distant relatives, suggesting that some phenotypic modifiers are shared only among close relatives. Whether this effect reflects a shared genetic background, a common environment, or both remains unknown.

**XPD *Defects and Clinical Severity in TTD,*** *by Botta et al.* **(*p. 1036*)**

The *XPB* and *XPD* genes each encode subunits of the basal transcription-factor–complex TFIIH, and mutations in both of these genes can lead either to xeroderma pigmentosum (XP) or to the trichothiodystrophy (TTD). XP causes greatly increased rates of sunlight-induced skin cancer, whereas TTD is a developmental disorder that presents with brittle hair. TTD individuals are usually free from obvious skin symptoms, although some are extremely prone to sunburn. The absence of skin tumors in TTD is all the more surprising because TTD cells exhibit the same nucleotide-excision–repair defect that is observed in XP. Here, Botta et al. report clinical heterogeneity even among TTD individuals with lesions in *XPD*. The authors have ascertained and studied 11 Italian TTD individuals, and they find that the sensitivity of their cells to killing by UV is, in all cases, similar to that observed in XP cells, with no evident correlation between the XPD genotype and this cell-culture phenotype. They note, however, that the clinical features of TTD, including growth retardation and mental retardation, are most severe in individuals who carry one presumed null allele ("functional hemizygotes") as well as a weak allele.

***Attitudes of Deaf Adults toward Genetics,*** *by Middleton, et al.* **(*p. 1175*)**

Deafness is traditionally viewed as a disability, but deaf people often regard their condition more positively, as an aspect of their identity that gives them access to a unique linguistic subculture, the Deaf community. Because of this difference in perception, deaf people may regard the motivations of genetic researchers and counselors with suspicion, and they may consider the birth of congenitally deaf children as desirable or even preferable. Middleton and colleagues have tried to measure the extent and nature of such attitudes in deaf individuals. Here, they show that respondents at an international conference on the deaf (all of whom were hearing impaired, whether or not they were deaf at birth) generally applied negative descriptors to genetic testing and to discoveries in human genetics. This hostility was still more pronounced among those who describe themselves as belonging to the Deaf culture. Nonetheless, some respondents indicated that they would be interested in prenatal testing for deafness, and, of these, a few expressed a preference for having deaf children.

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