This Month in the *Journal*

ALK-1 Mutations in HHT Type 2, *by Berg et al. (p. 60), and* ***Endoglin Mutations,*** *by Shovlin et al. (p. 68)*

Two papers this month address the molecular basis of hereditary hemorrhagic telangiectasia (HHT), a vascular disorder that leads to spontaneous bleeding in numerous tissues. The two major genes that are associated with this condition, *HHT1* and *HHT2,* each encode transmembrane proteins that participate in signaling through receptors of the TGFβ receptor family. *HHT1* encodes endoglin, a protein that binds at least two ligands related to TGFβ; endoglin appears to alter the cellular response to these ligands. Likewise, *HHT2* encodes activin receptor–like kinase 1, ALK1, which, in the presence of a TGFβ receptor, binds a similar set of ligands. Shovlin et al., working with *HHT1,* and Berg et al., working with *HHT2,* have defined the genomic structure of their genes of interest and have identified multiple novel mutations. Both forms of HHT are dominantly inherited, and both nonsense and missense mutations have been found in each gene. Both groups found alleles that encode premature stop codons in which the mRNA is apparently too unstable to be detected. Hence, these groups argue that the genes act through haploinsufficiency. The two related genes lead to the same phenotype when mutated, and mutations in each appear to function in analogous ways to cause HHT. However, *HHT1* and *HHT2* must not be entirely redundant, because there is no cross-complementation between the two genes. Subtle differences in either their expression patterns or ligand specificities may provide an explanation.

Autosomal Recessive Hypohidrotic ED, *by Munoz et al. (p. 94)*

The *EDA* gene on the X chromosome is well established as a basis of the recessive disease hypohidrotic ectodermal dysplasia (HED), but the existence of other causal loci has been uncertain. HED presents in males with an absence of sweat glands and with abnormal tooth and hair morphology; carrier females are typically affected only in having small skin patches, the lines of Blaschko, which mark regions of differential X-chromosome inactivation. Over the past 30 years, several groups have described families in which both men and women are affected over their whole bodies, which is consistent either with autosomal transmission of the disorder or with skewed X inactivation. Munoz and coworkers now show that in five families with fully affected women, linkage and mutational analysis exclude association of HED with the *EDA* gene. They suggest that the autosomal gene involved in these families may be a homologue of one of two known genes identified in mice with a similar condition.

Friedreich Ataxia GAA-Repeat Expansion, *by Monrós et al. (p. 101)*

Anticipation refers to the tendency of an inherited disease to manifest more severely or at an earlier age as it is transmitted to successive generations in a family. This pattern correlates, in a number of dominantly inherited disorders, with increasing length of trinucleotide repeats (TNR) in a disease gene. The *X25* gene, associated with Friedreich ataxia (FA), is unique among the known TNR-carrying disease genes in that FA behaves as a recessive disorder, with long TNR tracts found in weakly expressing or null alleles. Now Monrós and colleagues show that the transmission of FA does not follow a consistent pattern of anticipation. In a set of 212 parent-offspring transmissions, they find that repeat-length changes are strongly influenced by the sex of the parent of origin. Mother-to-child transmissions may lead to either TNR expansion or TNR contraction, whereas father-to-child transmissions generally involve TNR contraction.

Human Gene Mapping Using GMS, *by Mirzayans et al. (p. 111)*

Linkage analysis aims to identify loci that are identical by descent (IBD) among affected individuals, and it generally involves scanning through the set of DNA samples, with markers that cover the whole genome. Genomic-mismatch scanning may provide a shortcut to this process by reducing the number of markers needed to probe a large set of DNAs. This novel method takes advantage of the fact that chromosomal regions that are IBD over several generations will typically be free of sequence mismatches. By using solution hybridization on DNA samples taken from two related individuals and by applying a series of enzymatic treatments to these DNAs, it is possible to generate heteroduplexes of the two original samples and to eliminate duplexes that carry mismatches. The resulting DNA preparation is enriched for sequences that are IBD, and markers that are linked to a gene of interest will be retained in this enriched preparation. Mirzayans et al. have used this approach to map a gene for iridogoniodysgenesis anomaly, using DNA samples from two distantly related affected individuals; their results are consistent with standard linkage analysis. The authors also discuss several potential sources of artifacts in this method.

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Extracolonic Cancers in HNPCC, *by Jäger et al. (p. 129)*

At least four different genes that participate in DNA mismatch repair are implicated in hereditary nonpolyposis colon cancer (HNPCC). The products of these genes are believed to act in concert, and certain alleles of these genes can act in a dominant-negative fashion to compromise DNA repair. Jäger et al. report here on the spectrum of mutations associated with an altered splicing allele of one of these genes, *hMLH1*. This mutant form encodes a highly unstable mRNA and is predicted to represent a null allele. Consistent with the model of genetic interaction, HNPCC patients who carry this allele exhibit a narrower range of cancers outside the colon than do carriers of other more highly expressed mutant alleles of either *hMLH1* or the other genes in this group.

Familial Skewed X Inactivation, *by Pegoraro et al. (p. 160)*

The paternal and maternal X chromosomes are normally inactivated randomly in women's tissues, but skewed patterns of X inactivation can occur. Typically, these lead to no harmful effects, but they can become significant through interactions with mutations on one X chromosome. Here, Pegoraro and coworkers report on a family with an X-linked myopathy that arises from a defect in the *dystrophin* gene. In this family, the normally X-linked recessive disorder is observed in female carriers, a result of dramatically skewed X-inactivation patterns. The authors followed the phenotype of preferential activation of the paternal X chromosome through this four generation pedigree, and they identified in Xq28 a 800-kb deletion that associates consistently with this trait. Affected women in this family are prone to a high rate of spontaneous abortion. It is unknown whether abnormal pregnancy is causally related to the X-inactivation phenotype, or whether it identifies this pattern of clinical and chromosomal findings as a novel contiguous gene–deletion syndrome.

$Fc_\varepsilon R1$-β Polymorphism and Serum IgE Levels, *by Palmer et al. (p. 182)*

Serum IgE is a defense mechanism used by mammals to suppress infections by multicellular parasites such as helminthic worms. Where there is little exposure to such parasites, IgE's role in causing atopic diseases such as asthma and eczema is more evident clinically, and high serum levels of this immunoglobulin predispose to these disorders. Curiously, the same high levels of IgE do not usually lead to atopy in groups of people who are exposed to high levels of helminths in their environment. Palmer and colleagues have examined the genetic linkage of serum IgE levels in a group of Australian Aborigines known to be endemically infected with hookworm and tapeworm. They find that in this group the high-IgE phenotype associates with markers in the gene for an IgE receptor protein, $Fc_\varepsilon R1$, as seen previously in urban Caucasian people. The authors suggest that atopy and a robust response to parasites may be different manifestations of the same genetic predisposition.

Generalized Relative Risk Ratios and QTL Study Design: I and II, *by Gu and Rao (pp. 200 and 211)*

In mapping quantitative-trait loci, the method of choice for achieving the greatest degree of statistical power may be extreme discordant sib-pair (EDSP) analysis, but the loss of data that comes from analyzing only sib pairs with extreme and discordant phenotypes can make such studies expensive. As an alternative, Gu and Rao have proposed to study sib pairs with extreme phenotypes, whether discordant or concordant, using what they call the "EDAC" method. They showed previously that, as long as the number of discordant pairs is kept even with the number of concordant pairs, EDAC is relatively powerful and may be more cost-efficient than EDSP. In this pair of papers, they consider how to optimize study design to maximize power and efficiency with a given data set. In the first paper, they develop the concept of generalized relative risk, a measure of the genetic contribution to a quantitative trait, and they use this parameter to estimate the amount of data needed to achieve a desired level of statistical power. In the second paper, the authors consider how to define the range of normal versus extreme values for a quantitative trait, to make EDAC or EDSP analysis optimally cost-efficient.

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