This Month in the *Journal*

This month, four reviews focus on genetic aspects of human sexual development. Roberts et al. (p. 933) consider a number of molecules that have been implicated in human or mouse gonadal dysgenesis or sex reversal. They note that some aspects of the sex-determination pathway appear to be conserved, even in invertebrate species. However, at least one crucial feature of the pathway that has been deduced from sex reversals in humans—that is, the sensitivity to dosage of genes for various regulatory molecules—is not observed in strains of mice with targeted mutations. Rugarli (p. 943) discusses the cellular basis of Kallmann syndrome, a remarkable X-linked developmental disorder that presents with hypogonadism and a complete absence of the sense of smell. Latronico and Segaloff (p. 949) review the biochemistry of G-protein–coupled receptors, particularly the leutinizing-hormone receptor (LHR), which activates gonadal development. They consider the effects of naturally occurring human *LHR* mutations, both hyperactivating and inactivating, on the structure and the interactions of the LHR, and they discuss the effects of these mutations on the timing and progression of puberty in males and females. Finally, Davey et al. (p. 959) discuss the JAK/STAT signal-transduction pathway, focusing on the role of STAT5, for which they have developed a mouse knockout model. In at least some mammalian species, STAT5 mediates the differential effects of pulsatile or continuous exposure to growth hormone that lead to male-specific and female-specific patterns of gene expression.

Mosaicism and AR Expression in SBMA, *by Tanaka et al.* **(***p. 966***)**

CAG trinucleotide-repeat tracts are well known to undergo expansion and contraction between generations, but their stability within the soma of a single individual is not as well studied. Tanaka et al. have observed tract-length mosaicism in the CAG repeat that is found in the androgen receptor (*AR*) gene, and they report a striking correlation between the expression of the gene and the level of variability in a tissue. The instability of this sequence in muscle and testis cells, among others, and its relative stability in nervous tissue are specific for this gene. Other CAG-containing genes, the Huntington disease (*HD*) and dentatorubural-pallidoluysian atrophy (*DARPLA*) genes, are expressed in the CNS, and their CAG tracts are relatively unstable in brain cells. The effect of transcriptional activity on replication fidelity may be understood if the passage of RNA polymerase through the CAG tract promotes mispairing, as has been found in some studies of bacterial DNA replication. Alternatively, the effect may reflect the influence of an active chromatin structure on the tertiary structures that the CAG tract can adopt.

Germline* TP53 *Mutations and Childhood Adrenocortical Tumors, *by Varley et al.* **(***p. 995***)**

The tumor-suppressor gene *TP53* is associated with the multisystem familial-cancer disorder Li-Fraumeni syndrome (LFS). Although LFS-associated mutations appear to be highly penetrant, low-penetrance alleles of *TP53* might be expected in other cancer syndromes. Here, Varley and colleagues show that children with tumors of the adrenal cortex carry germline mutations in *TP53* at a remarkably high rate. Although some of their family histories show an unusually high incidence of cancer, germline transmission through individuals with neither LFS establishes that the mutations are of limited penetrance. This group of 14 subjects was ascertained by the presence of adrenocortical adenomas or carcinomas in the absence of typical LFS. In at least 10 cases, these children carried germline *TP53* mutations, predominantly one of two missense mutations that are predicted to affect the DNA-binding domain of TP53. Indeed, these authors have recently published evidence that the product of one of the missense alleles fails to transactivate target genes in a heterologous system. Because this gene is implicated in the cellular response to DNA damage following ionizing radiation, the present findings have immediate implications for the treatment of this class of tumors in children. Three of the individuals studied here underwent radiation therapy for their primary tumor and developed secondary tumors in the radiation field within 2 years.

RB *Mutations Linked to Low Penetrance,* *by Otterson et al.* **(***p. 1040***)**

The high penetrance and dominant transmission of retinoblastoma were crucial in developing the understanding that loss of heterozygosity in tumor-suppressor genes causes familial cancers. In most families with germline mutations in the *RB* gene, the disease affects both eyes of all heterozygous individuals. However, some families with RB include unaffected carriers and people with tumors in only one eye, as well as bilaterally affected individuals. Several regulatory or structural mutations in *RB* have been found that confer this low-penetrance ef-

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fect, and Otterson and colleagues have now surveyed 12 families with low-penetrance disease. Here, they identify three mutations, one of them novel, all of which affect the pocket of the protein that mediates binding to the SV40 T antigen. All three of the variant proteins are expressed, and all retain some biological activity, as seen by their ability to undergo cyclin-dependent phosphorylation in cell-culture experiments. However, protein-protein interactions mediated by the RB pocket appear to be unstable in cells expressing the mutant RB cDNA, and the authors use the yeast two-hybrid system to demonstrate that these interactions are temperature-sensitive. These mutant alleles probably confer levels of activity that are adequate to allow for normal cell-cycle control, even in hemizygous cells, but Otterson et al. speculate that some intracellular conditions, probably not involving elevated temperature, cause tumors by further reducing this already weakened activity.

Joint Qualitative-Trait/Quantitative-Trait Multipoint Linkage Analysis, *by Williams et al.* (*p. 1134*) *and* ***Alcoholism and Event-Related Potentials,*** *by Williams et al.* (*p. 1148*)

In the first of this pair of papers, Williams et al. develop the variance-components approach to linkage analysis, allowing the modeling of the correlation between distinct traits. The authors note that, when such traits represent different aspects of a single genetic condition, this multivariate approach is often more powerful than linkage analysis of either trait independently. The method that has been developed here allows the authors to study pairs of traits, one qualitative, such as the presence or absence of a disease, and the other quantitative. Using simulated data that were developed to model a pair of correlated traits, they show that, when evidence of linkage to the expected loci in single-trait analyses fall short of significance, it can be strengthened by mapping the correlated data. The second paper applies the method to the mapping of alcohol dependence and a quantitative neurophysiological trait, the so-called "P300 event-related potential" (ERP). The relationship between alcoholism and this trait is not understood mechanistically, but the value of this ERP is reported to be low both in alcoholics and in members of their families who, although abstinent, are at increased risk of alcoholism. Williams et al. make use of the extensive genotypic and phenotypic data from the Collaborative Study on the Genetics of Alcoholism. They analyze 105 families in which alcoholism is seen in one of the parents in a founding generation. By bivariate analysis of this quantitative trait along with the binary trait of alcoholism, the authors confirm earlier findings of an alcoholism locus on chromosome 4, close to the *ADH3* gene. The finding that the ERP phenotype is linked to this locus may indicate that *ADH3* or some neighboring genes influence drinking behavior by their effects on neurophysiology, rather than by altering the metabolism of alcohol in the liver and elsewhere.

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