This Month in the *Journal*

Duplication of 7p11.2-p13 in SRS, *by Monk et al.* **(***p. 36***)**

Silver-Russell syndrome (SRS) is characterized by pre- and postnatal growth failure, as well as by certain other dysmorphic features, including a triangularly shaped face and lateral asymmetry. Maternal uniparental disomy of chromosome 7 (mUPD7) has been identified in some cases of SRS, suggesting that genetic imprinting plays a causal role in the disorder. However, it is unclear whether the phenotype results from the duplication of a maternally expressed gene or from the absence of a paternally expressed gene. The proband presented by Monk et al. possesses a tandem duplication of 7p11.2-p13. Haplotype analysis identifies this duplication as maternal in origin. The presence of a maternal duplication in the proband, who carries a normal paternal chromosome 7, suggests that SRS results from overexpression of a maternally expressed, imprinted gene. Fine mapping indicates that the duplication in this proband includes the gene for GRB10, a growth-factor receptor–binding protein that has been proposed as a candidate for *SRS*. The growth-suppressing action of GRB10 is consistent with the phenotype of SRS, which is characterized by growth retardation. Furthermore, an asynchronous replication pattern was found for *GRB10,* suggesting that it is indeed imprinted, as predicted.

Mosaicism in von Hippel–Lindau Disease, *by Sgambati et al.* **(***p. 84***)**

von Hippel–Lindau disease (VHL) is an autosomal dominant disorder characterized by malignant and benign tumors, particularly of the retina and CNS. Approximately one-quarter of cases of VHL occur spontaneously. Although some of these spontaneous cases result from germline mutations in unaffected parents, Sgambati et al. have shown that other spontaneous cases result from postzygotic mutations. This leads to somatic mosaicism and, if the germline is affected, to transmission of the mutation to children. The potential for parental mosaicism is therefore an important consideration when one is handling de novo cases of VHL. First, mosaic individuals may require counseling on the risk of transmission of the mutation to future offspring. Second, because individuals with somatic mosaicism for a VHL defect are themselves at risk for VHL, they may benefit from early detection and treatment of lesions. Since somatic mosaicism is easily missed when testing is done by standard methods, such as Southern blotting or DNA sequencing using lymphocytes, it is therefore important to use more-thorough screening methods. Tissues in addition to lymphocytes can be sampled, and alternative approaches, such as FISH and conformation-sensitive gel electrophoresis, may be used to improve the odds of identification of at-risk, mosaic individuals.

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Heme Oxygenase and Pulmonary Emphysema, *by Yamada et al.* **(***p. 187***)**

Although smoking is an obvious risk factor for chronic pulmonary emphysema (CPE), the question remains as to why only a small percentage of long-term smokers actually suffer from this disease. One explanation holds that there is a differential sensitivity to the free radicals in cigarette smoke, which damage lung tissue. The antioxidant heme oxygenase 1 (HO-1) protects lungs from oxidant-mediated tissue damage, potentially involving HO-1 in this process. Yamada et al. establish a link between expression of *HO-1* and the development of CPE. A polymorphic $(GT)_n$ repeat in the 5′-flanking region of human *HO-1* has been identified that modulates *HO-1* transcription. Examining matched cohorts, the authors show a correlation between the length of this repeat and the presence of emphysema; smokers with CPE have a higher frequency of long repeats in this region than do smokers without CPE. In vitro transcription studies in cell lines expressing *HO-1* show that transcription of *HO-1* varies inversely with the length of this GT tract, providing a likely mechanism for this correlation. Decreased production of HO-1 due to a longer 5′-flanking region could compromise the lung's capacity to combat the free radicals in smoke and could explain the correlation between repeat length and CPE. These results support the theory that an excess of free oxygen radicals in cigarette smoke damages the lungs and initiates CPE development. Furthermore, the results suggest that an individual's *HO-1* genotype can influence the degree to which the lung damage occurs and, thus, the risk for CPE.

12q-Telomere Biology and Human Evolution, *by Baird et al.* **(***p. 235***)**

Comparisons of the telomeric junctions of human chromosomes to orthologous sequences in higher primates suggest that at least some human telomeres emerged following the evolutionary divergence of the *Homo* and *Pan* lineages. Now, Baird et al. have sequenced the 12q and Xp/Yp telomeres and telomere junctions and have

identified polymorphisms that allow them to define distinct haplotypes that extend from the subtelomeric regions into the telomere repeat sequences. Linkage disequilibrium between these polymorphisms suggests a suppression of recombination in this region. Interestingly, intermediate haplotypes, representing the sequential mutations required to produce the divergent haplotypes, were not identified. The lack of intermediate haplotypes suggests that the extant haplotypes did not arise through random genetic drift but, rather, that they might have arisen through the hybridization of two hominoid lineages, at a point during the evolution of modern man.

Genetic Information and Health Insurance, *by Hall and Rich* **(***p. 293***)**

Fear of genetic discrimination by insurers greatly influences both the decision to have genetic testing performed and, therefore, the widespread utilization of genetic testing. Several state and federal laws prohibit insurers from applying a "preexisting condition" designation to healthy individuals who carry a predisposing allele for a genetic disorder. However, it is unclear how well these laws work. Hall and Rich tackled this problem through interviews with both medical and health-insurance professionals. They examined whether genetic-testing results have been considered in insurance underwriting, either before or after these laws were passed. Surprisingly, there was no evidence that insurers were interested in presymptomatic genetic conditions, either before or after this legislation, nor did they appear to take advantage of differences in state antidiscrimination laws. On the other hand, these laws have made medical professionals and patients more concerned about the use of genetic-testing information. One might conclude, therefore, that the genetic-discrimination laws have been premature. However, these laws have influenced social attitudes against genetic discrimination. These attitudes will be important in the future, as genetic testing becomes more prevalent and more predictive.

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