# This Month in the *Journal*

This month in the *Journal,* Spence et al. contribute an opinion piece on what they see as current problems in statistical genetics. Specifically, they denounce the focus on the most popular statistical designs (to the exclusion of other useful methods) without thought to the appropriateness of the method or the extent to which the methods have been tested. They hope this piece will serve as a starting point for discussions in this area, and they have suggested some ways they think these problems might be addressed.

**KLOTHO *Allele Status and Occult CAD,*** *by Arking et al.* (*p. 1154*)

An allele of *KLOTHO* called "KL-VS" has previously been associated with reduced human longevity. This association, in addition to the fact that *Klotho*-deficient mice have extensive arteriosclerosis, led Arking et al. to see whether the KL-VS allele influences risk for atherosclerotic coronary artery disease (CAD). Two samples of apparently healthy siblings of hospitalized index cases with early-onset CAD were collected and given a full cardiovascular and physical exam to look for occult CAD. In the first sample, which was made up mostly of whites, the KL-VS allele was a significant risk factor for occult CAD, and the detrimental effect of the allele was more pronounced in normotensive individuals. Although the effect was not as pronounced, the KL-VS allele also influenced risk of occult CAD in the second, African American, sample. Klotho is a glycosidase, but its substrate has not yet been identified. However, impaired endothelium-dependent vasodilation, decreased nitric oxide (NO) metabolites, and impaired angiogenesis are seen in *Klotho*-deficient mice, suggesting that Klotho may protect the cardiovascular system through endothelium-derived NO production. Since ~25% of individuals are carriers of KL-VS, it may turn out to be an important risk factor for CAD.

***Genomic Signature of Radiation Exposure,*** *by Hande et al.* (*p. 1162*)

Hande et al. wanted to measure the level of stable chromosomal rearrangements resulting from exposure to densely ionizing radiation, such as alpha particles and neutrons. To do this, they collected blood from individuals who received exposure to plutonium while working at a nuclear facility in the Soviet Union. As comparison groups, they had people who had been exposed to sparsely ionizing gamma rays and an unexposed group. Through use of a combination of mFISH and mBAND, they were able to find intra- and interchromosomal rearrangements in the cells of these individuals. Intrachromosomal aberrations were found at a much higher frequency in the workers who had been highly exposed to plutonium than in the other groups, and the number of aberrations per cell correlated with the estimated plutonium dose to the bone marrow. Staining for intrachromosomal rearrangements was done only on chromosome 5 in these experiments, and extrapolations of these data across the genome give an estimate of 62% of cells having a detectable intrachromosomal aberration, despite the fact that these individuals are healthy.

***Triallelic Inheritance in* BBS1,** *by Beales et al.* (*p. 1187*)

Recent evidence has indicated that a combination of three mutations at two loci may, in some cases, be required for the development of Bardet-Biedl syndrome (BBS). The majority of the known BBS loci are believed to participate in this complex form of inheritance. However, initial reports of the most common BBS locus, *BBS1,* suggest that it does not. Beales et al. pool their resources to study the role of *BBS1* in the development of disease. In contrast to previous findings, their sample does provide evidence that *BBS1* is involved in complex inheritance, including the fact that there were families with three mutations at two loci, one of which was *BBS1*. In addition, unaffected individuals with two *BBS1* mutations were identified, suggesting that additional genetic variation may help determine whether or not disease develops. Finally, the most common *BBS1* mutation, M390R, was found at an elevated carrier frequency in a sample of control subjects. On the basis of this observed frequency, if BBS were simply autosomal recessive, the prevalence of BBS would be ~10 times higher than is observed. Further studies are needed to determine how the BBS loci work together to cause disease.

***Native American Y Chromosomes in Polynesia,*** *by Hurles et al.* (*p. 1282*)

Although it is clear that the islands of Southeast Asia contributed to the settlement of Polynesia, there are Native American lineages present in Polynesia, as well. Whether these represent the mutual retention of shared Asian sequences or whether there was limited prehistoric gene flow between these populations has not been determined. Hurles et al. combine mtDNA and Y chromo-


0002-9297/2003/7205-0001$15.00

some analysis along with historical information to reconstruct the forces that led to the current genetic composition of the Polynesian island of Rapa. There are only 16 unrelated, indigenous paternal lineages currently on Rapa, and, within these, evidence for significant European and Native American male-mediated admixture can be found. In the 10 typically Polynesian Y lineages, there is greater genetic diversity than expected. In contrast, no evidence of Native American influence is found in the 18 unrelated mtDNA sequences, nor is there elevated diversity in these lineages. Historical information indicates that, in the 19th century, the population of Rapa went through a severe bottleneck that reduced the population by >10-fold. This bottleneck resulted from an epidemic following the repatriation of Polynesian slaves from Peru. Hurles et al. use information gleaned from historical records of that time to account for the current genetic landscape of the island. They found that some crew members of the slave ships remained on Rapa and may have contributed European and Native American lineages to the population. Further, repatriated slaves were dropped on Rapa regardless of their island of origin and are known to have contributed to the Rapan gene pool, which would have contributed to its elevated diversity. The authors suggest that, before attempting to study the prehistory of populations, researchers should first look at modern history to see how these populations may have been shaped.

**GARS *Mutations in CMT2D and dSMA-V,*** *by Antonellis et al.* (*p. 1293*)

It has been proposed that Charcot-Marie-Tooth type 2D (CMT2D) and distal spinal muscular atrophy type V (dSMA-V) are allelic diseases, because of their similar phenotypes and their colocalization on chromosome 7p. Both are peripheral neuropathies that more severely affect the upper extremities. In this work by Antonellis et al., genotyping of the chromosome 7p locus was performed on five families with either phenotype, and the critical region was narrowed to ~980 kb. Sequence of this region revealed missense mutations of *GARS,* which encodes the glycyl tRNA synthetase gene, in all five families, confirming that CMT2D and dSMA-V are allelic. This is the first aminoacyl tRNA synthetase defect associated with a genetic disease. The authors speculate as to how a general translation defect manifests as such a specific phenotype.

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