This Month in *The Journal*

Robin E. Williamson[1]

Birk Barel Syndrome Due to a Mutation of an Imprinted Gene

Barel et al., page 193

Genomic imprinting results in the expression of only one allele, either the maternal or the paternal, of certain genes. As a result of this phenomenon, if a mutation in the maternal copy of a disease-related paternally silenced gene occurs, no wild-type copy will be expressed, and the carrier individual will present with the disease. In contrast, if the paternal copy of the same gene is defective, the individual will not have the disease. Imprinting can, therefore, lead to disease pedigrees with apparent non-Mendelian forms of inheritance. Barel et al. study a family with mental retardation and hyperactivity that appears to be transmitted via a defect in a paternally silenced gene. Linkage analysis points to a region on chromosome 8 that harbors the known imprinted gene, *KCNK9*. *KCNK9* encodes a potassium channel, and sequence analysis identifies a missense mutation that segregates in the expected manner. The affected residue is predicted to interfere with channel conduction, and functional analyses in *Xenopus laevis* oocytes reveals a lack of current production in mutant channels.

Genetic Epidemiology of Deafness

Arnos et al., page 200

Assortive mating has long been recognized as a characteristic of the deaf community, and there was early speculation that such restricted mating would result in the increase in frequency of deafness-associated mutations. As more deaf individuals marry other deaf individuals and have children, mutations causing deafness would become more prevalent in the deaf population. Previous simulation work predicted that the frequency of the most common form of recessive deafness, DFNB1, might have doubled in the last two centuries. To empirically measure this value, Arnos et al. compare data from a contemporary population of deaf individuals with those collected from a special study initiated more than 100 years ago. In 1898, Edward Allen Fay recorded information from 4471 marriages of deaf individuals and assembled a dataset of three-generation pedigrees. The number of pedigrees with recessive deafness in these groups is estimated from the number of noncomplementary matings. A mating is considered noncomplementary if two individuals who are deaf have a child who is also deaf. It is then assumed that the two parents each carry a mutation in the same gene. The percentage of noncomplementary matings in the earlier dataset was 4.2%. The same measurement for the modern group is 23%. Because DFNB1 is the most common form of recessive deafness, the authors predict that the 5-fold increase in noncomplementary matings is due to an increase in the prevalence of mutations causing DFNB1.

Olfactory Receptor Copy-Number Variation

Young et al., page 228

Our ability to perceive odors is based on a multitude of olfactory receptors (ORs) that recognize odorants. Through the use of a combinatorial mechanism, humans have the ability to detect more odors than the number of receptors expressed. This large repertoire exists in humans even though approximately half of OR genes have evolved to be nonfunctional pseudogenes. As might be expected, the percentage of pseudogenes in rodents and dogs is much lower, and researchers speculate that selection in these species has maintained a higher number of functional ORs. OR genes are found in clusters in the genome and are often within regions of segmental duplications (SDs). With the current close inspection of regions of copy-number variation, many investigators have observed that ORs are highly frequent in copy-number-variable regions (CNVRs). Young et al. examine reliable and high-resolution CNVR data to find out whether there is a direct relationship between ORs and CNVRs or whether the association is due to the more indirect fact that ORs are in SDs and that SDs are in CNVRs. The authors report that there are significantly more ORs in CNVRs than expected. They also compare the percentage of functional ORs with that of pseudogenes in the CNVRs and suggest that the association between ORs and CNVRs is probably not due to positive selection but is more likely due to the selection against CNVRs in other genomic regions where dosage-sensitive genes reside.

mtDNA Mutation Prevalence

Elliott et al., page 254

Phenotypes due to mutations in mtDNA are often not clinically significant until the amount of mutant mtDNA

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passes a critical threshold. Several generations of individuals may carry low levels of mutant mtDNA molecules without disease until an individual inherits a higher level and presents clinically. This dependence of disease presentation on heteroplasmy percentage makes the determination of who is carrying mitochondrial mutations difficult. It is possible to screen the maternal relatives of an affected individual to establish their carrier status, but this doesn't contribute to estimating the prevalence of carriers in the general population. Elliott et al. study a set of about 3000 samples collected sequentially to address this question. By using sensitive analyses that can detect very low levels of mutant mtDNA, the authors screen the samples for ten common pathogenic mtDNA mutations. Fifteen individuals who carry one of five of the mutations are identified. Twelve of these individuals are heteroplasmic, and comparison to maternal samples establishes a rate of de novo mtDNA mutations in the dataset.