This Month in *The Journal*

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Natural Selection and Human miRNAs

Quach et al., page 316

Ribonucleic acid (RNA) is the material from which proteins are encoded. However, not all RNA contains the codes for protein building. Micro RNAs (miRNAs) are one such class of noncoding RNA molecules. As the name implies, miRNAs are small, only about 22 nucleotides long, and have been found to silence gene expression. They do this by base pairing with protein-coding RNA, making a double stranded complex that cannot be translated. To date, around 70 complex diseases have been reported to be associated with some of the 1000+ predicted miRNA molecules. Although disease associations continue to be made, not much is known about the evolutionary forces acting on this group of molecules. To help elucidate possible modes of selection acting on miRNAs, Quach and colleagues resequence 117 miRNAs, chosen from the miRBase database, in several different human populations. The study is designed to detect polymorphisms and thereby gather information regarding the evolution of miRNAs. The authors find that miRNAs have less variation than the general genome, particularly within the first 14 nucleotides. They also find that a limited number of miRNAs have undergone positive selection. These findings will aid in the understanding of how miRNAs are involved in complex diseases.

Genome-wide Analysis for Otosclerosis

Schrauwen et al., page 328

Otosclerosis is defined as excessive bone growth within the middle ear. This abnormal bone growth interferes with the function of the stapes, also know as the stirrup, leading to impaired sound transmission and hearing loss. Otosclerosis is the most common known cause of hearing impairment. There are many different forms of otosclerosis, attributed to different genetic loci; however, few causative genes have been identified to date. Although otosclerosis is thought to be transmitted in an autosomal-dominant fashion, incomplete penetrance suggests a combination of environmental and genetic factors. To identify genes contributing to the phenotype of otosclerosis, Schrauwen and colleagues conduct a genome-wide association study (GWAS). By pooling DNA samples from nearly 700 Northern Europeans, the authors identify an association between mutations in *RELN* and otosclerosis. The association is confirmed in a French population. The mouse ortholog of *RELN* is known to be involved in neuronal migration, and a similar function can be expected in humans. Although *RELN* is expressed in human stapes and *Reln* in mouse cochlea, the role of RELN in otosclerosis is not yet clear.

Stress-Induced Copy-Number Changes

Arlt et al., page 339

The human genome consists of numerous repetitive sequences that have variable copy numbers in different individuals. These so-called copy-number variants (CNVs) confer genetic variation and often phenotypic differences in different populations of people. The term copy-number change (CNC) refers to those duplications and deletions in the genome (CNVs) that lead to genetic disorders. CNCs vary in size and arise sporadically. The mechanism by which pathogenic CNCs arise has been largely unknown. In a study by Arlt and colleagues, a likely common mechanism of CNC formation has been elucidated. Using normal human fibroblasts, the authors show that replication stress can induce a wide array of CNCs in mitotically active cells. They further characterize the duplication and deletion break-point junctions of the CNCs and find short microhomologies of sequence at these sites, indicating that nonhomologous end joining or template switching are the likely mechanisms of CNC formation.

HTT Haplogroup in Huntington Disease

Warby et al., page 351

Huntington disease (HD) is caused by expansion of the CAG repeat in *HTT*. Although the number of triplet repeats is variable in the population, an allele with more than 36 copies leads to the autosomal-dominant neurodegenerative disorder. The basis for the triplet expansion is incompletely understood, but previous evidence supports that paternal transmission and environmental factors can increase the risk of repeat expansion. Studies have also suggested that there may be genetic elements that work in *cis* or in *trans* to affect repeat stability. In an effort to identify *cis* factors that contribute to CAG expansion, Warby et al. analyze SNPs in the *HTT* region to see whether any are

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associated with expanded alleles. The frequency of these SNPs on disease alleles is first compared to that of the SNPs on control alleles. Many SNPs are significantly associated with the HD chromosomes, but markers in intervening regions are not, which leads the authors to suggest that the observed associations between SNPs and disease chromosomes are not due to a founder effect but may be causative in nature. This hypothesis is further supported when alleles of increased, but not yet pathogenic, size (27–35 repeats) are included in the analysis. The haplogroup that serves as a sensitive marker of disease chromosomes is also enriched on these intermediate alleles as compared to control alleles. The authors suggest that this haplogroup is a predisposing risk factor for *HTT* repeat expansion.

Mutations in *SPATA7* Cause LCA and RP

Wang et al., page 380

Leber congenital amaurosis (LCA) is a genetically heterogeneous eye disorder, and mutations in genes from a number of functional pathways have been found to cause the disease. The LCA phenotype is related to retinitis pigmentosa (RP), but it has an earlier onset and is more severe. Several of the genes involved in LCA have also been linked to RP and other retinal diseases. In addition, there are two LCA loci for which the gene has not yet been identified. One of these, LCA3, is on 14q24 and was originally mapped in a large consanguineous family from Saudi Arabia. Here, Wang et al. report findings from their study of additional patients linked to the LCA3 region. The authors are able to define, through the use of homozygosity fine mapping, a critical region that includes nine genes. Homozygous loss-of-function mutations in *SPATA7* are found in patients with LCA or juvenile RP. The patients are from a variety of ethnic backgrounds. Although the function of *SPATA7* is unknown, Wang et al. use in situ hybridization and immunohistochemistry to evaluate gene and protein expression in the developing and mature mouse retina. Expression is very low at early stages, but high levels are detected in the mature retina. The authors suggest that *SPATA7* plays a role in eye function as opposed to being involved in eye development.