This Month in *The Journal*

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Mutations in *C2orf37* Cause Woodhouse-Sakati Syndrome

Alazami et al., page 684

Woodhouse-Sakati syndrome (WSS) is a multisystem disorder that is characterized by hypogonadism, alopecia, diabetes, mental retardation, and ECG abnormalities. The syndrome affects a number of families in Saudi Arabia, and Alazami et al. begin their search for causative alleles in these families. Gene mapping identifies a homozygous base-pair deletion in *C2orf37*, a hypothetical gene on 2q, in all affected Saudi patients studied. Different homozygous mutations in *C2orf37* are then identified in additional patients from Eastern Europe, India, and the Middle East. Although very little is known about the gene and the protein contains no known domains, strong conservation across species suggests that the protein has an important function. Additionally, because WSS involves a number of organ systems, the authors predict that *C2orf37* would be present in a number of the affected tissues. To further characterize the gene, Alazami et al. perform transcript analysis and find that multiple splice variants exist, of which two are considered predominant. Interestingly, only one of these two main transcripts is predicted to be affected by the Saudi and East European mutation. Localization work in mouse embryos reveals ubiquitous nucleolar expression, with evidence of increased levels in brain, liver, and skin. Functional assessment of the Saudi mutation suggests that a nucleolar defect is involved in the etiology of WSS, and this links the findings to reports that a clinically similar syndrome of alopecia, neurological defects, and endocrinopathy is caused by defects in a different nucleolar protein, RBM28, which is involved in ribosome biogenesis.

FMR1 Premutation in Adults Under Age 50

Hunter et al., page 692

Expansion of the CGG repeat in *FMR1* to more than 200 copies is the cause of fragile X mental retardation syndrome, but carriers of premutation alleles, expansions of 55–199 repeats, are also affected by certain phenotypic features. Male premutation carriers over the age of 50 have an increased risk of developing FXTAS, a disorder associated with tremor and ataxia, and a percentage of female premutation carriers suffer from primary ovary insufficiency. In addition to these established effects, there have been mixed reports of neuropsychological phenotypes in premutation carriers who are younger than 50 years old. Concerns about ascertainment bias, sample size, and control populations have contributed to questions about whether or not the *FMR1*-premutation allele is associated with neuropsychological features in younger males and females. In an effort to establish whether there is a relationship, Hunter et al. perform a number of neuropsychological assessments in a large group of men and women who are 18–50 years old and carry an *FMR1*-premutation allele. Statistical analysis and subject-recruitment strategies were designed to minimize factors contributing to false positives. The authors find that there is little influence of premutation status on an individual's performance on the neuropsychological tests. A small increase in symptoms associated with ADHD is observed in female premutation carriers, but no general association is observed between the premutation allele and neuropsychological phenotypes in carriers between 18 and 50 years old.

Admixture in the Iberian Peninsula

Adams et al., page 725

Cultural history is largely defined by changes in ruling populations through time and can be deciphered through the use of archaeology, place names, and linguistic elements. An emerging practice is for one to complement and enhance historic knowledge by analyzing the genetic history of a people or region. Genetic information not only clarifies demographic trends but can provide insight into social and religious practices of the governing people. Adams et al. sought to clarify the ancestry of people residing within the Iberian Peninsula and Balearic Islands. Like other European regions, Iberia is influenced by several different ruling peoples from diverse locations, cultures, and religions. Ancient Iberian history includes that of early Phoenician, Greek, Carthaginian, and Roman cultures. Within the Common Era, Iberia has been ruled by Christian Visigoths, Muslim Moors, and Catholic Monarchs following the Crusades. Although never a ruling people, Sephardic Jews have a long history in Iberia and originate from this region. By analyzing genetic similarities and differences within the Y chromosome of males currently living in the Iberian Peninsula and Balearic Islands, Adams

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et al. have found that their ancestry contains a disproportionate degree of North African and Sephardic Jewish contribution. These findings suggest that religious intolerance and conversion have contributed to the cultural and genetic history of this region.

Population Divergence Estimated from Linkage Disequilibrium

Sved et al., page 737

One focus of studies that look at the historical movements of people in the world is the determination of the time that different populations diverged from each other. It is accepted that a number of migrations out of Africa occurred, but it is more difficult to determine when each group separated from the others. There are established means of estimating the divergence times of more distantly related groups, but such methods do not work well between human populations. The success of methods that have been developed for use in humans has been limited by the requirement of knowing the effective population sizes at the time when the populations split. In an effort to avoid this requirement, Sved et al. introduce a method that is based on linkage disequilibrium (LD). They report that the population differences in the LD between markers are not related to the effective population sizes at the divergence time. The authors then use their method to evaluate the HapMap samples and compare the Yoruban population with the Asian populations, as well as the Yoruban samples with the European samples. Their assumption is that the LD in the Yoruban samples is similar to that of the ancestral population from which both the Asian and the European populations are derived. They estimate that, in accordance with other reports, Europeans diverged from the African population a few hundred generations later than Asians did.

The Identification of Additional Genes Mutated in Diamond-Blackfan Anemia

Gazda et al., page 769

Diamond-Blackfan anemia (DBA) is a congenital condition that is frequently diagnosed in patients before the age of one year. As in other kinds of anemia, the body does not create enough red blood cells. In DBA in particular, a bone-marrow defect is responsible for the low production of red blood cells. DBA patients suffer from many anemia-related symptoms, including fatigue and tachycardia. In addition, a significant proportion of patients also has short stature and congenital malformations. For now, treatment options are limited to steroids, blood transfusions, and bone-marrow transplantation. The effectiveness and risks associated with each of these treatments can vary. Familial cases of DBA are inherited in a dominant manner. To date, mutations in four different genes have been identified in about 30% of patients. The four genes, *RPS19*, *RPS24*, *RPS17*, and *RPL35A*, encode proteins that make up subunits of the ribosomes. Because of this involvement of ribosomal proteins in DBA, Gazda et al. decide to sequence additional ribosomal genes in a group of 196 DBA families. Numerous sequence variants are identified, and, of particular note, 24 individuals have mutations in *RPL5* and 18 carry a *RPL11* variant. To learn more about the disease caused by mutations in these genes, the authors compare the disease features with those of patients who have DBA due to mutations in other genes. The analysis suggests that the presence of mutations in *RPL5* or *RPL11* might contribute to additional symptoms and might also have an effect on treatment.