This Month in *The Journal*

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Abraham's Children in the Genome Era

Atzmon et al., page 850

Judaism predates the other primary Abrahamic religions, Christianity and Islam. Although Jewish heritage in the Middle East can be traced back to the second millennium BCE, the genetics of contemporary Jews is unsettled. As a result of a series of diasporas, Jewish communities spread from Israel and Judah to the Middle East, Europe, and Africa. As time and geographic distance has accrued, the matter of common Jewish genetic history has arisen. The question of whether current Jewish communities around the world share more than a religious background is tackled here by Atzmon and colleagues. This group has analyzed genetic ancestry of seven different Jewish groups established at different times and in different regions throughout the Middle East and Europe. Comparing these Jewish populations with non-Jewish reference populations, these authors find distinct clusters representing the major Diaspora groups, namely Ashkenazi, Sephardic, and Mizrahi. Within these groups, each individual Jewish population forms its own cluster, indicating that although Jews around the world do share genetic history tracing back to the Middle East, different populations can be distinguished. These findings can be extrapolated to provide dates and degrees of admixture. For example, Jews dating back to the Hellenic-Hasmonean times are less genetically similar to other Jews than are those originating from the Babylonian empire. This is attributed to the practice of proselytism during the Hellenic-Hasmonean time. Overall, this study illustrates that contemporary Jewish populations share both religious and genetic history.

Nonrecurrent Rearrangements in CMT1A and HNPP

Zhang et al., page 892

The neuropathies Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP) are caused by genomic rearrangements of 17p12. The disease outcome depends on the dosage of the region: duplications can cause CMT1A, and deletions can cause HNPP. Of the genes affected by these disruptions, there is a growing wealth of evidence that the perturbation of *PMP22* is responsible for the disorders. Although the vast majority of the 17p12 rearrangements are recurrent and due to nonallelic homologous recombination mediated by low-copy repeats, some cases are unique disruptions of atypical size. To learn more about these nonrecurrent rearrangements, Zhang and colleagues characterize the breakpoint sequences in a collection of such cases. A range of sequence elements are found at the breakpoints, and the authors are able to make predictions about which mechanisms had a role in creating some of the disruptions. The findings in each case also provide additional support for the conclusion that it is the disruption or dysregulation of *PMP22* that causes CMT1A and HNPP.

Controlling for Population Stratification in mtDNA-Association Studies

Biffi et al., page 904

The wealth of ancestry information contained in mitochondrial DNA (mtDNA) is often utilized in population studies, but its presence also requires that steps be taken to control for hidden population substructure when mtDNA is used in association studies. A number of methodologies have been developed to handle population stratification (PS) in autosomal data, but less focus has been given to ways to correct for PS when mtDNA is used. In this issue, Biffi and colleagues perform a comprehensive analysis of the effects of PS in mtDNA-association studies and evaluate the best strategies for controlling it. As a first step, the authors demonstrate that population structure at the autosomal level is not necessarily correlated with that of the mitochondrial genome; controlling for PS in the autosomal genome does not always remove the confounding due to population structure in mtDNA. They then compare the efficiency and the effectiveness of the methods currently being used for minimizing PS in mtDNA-association studies and propose that a new strategy is needed. Biffi and colleagues report that using principal component analysis (PCA) with mitochondrial markers is the best way to control PS in association studies using mtDNA, and they use real data to demonstrate how a signal deemed to be significant after correction via traditional methodology was concluded to be a false positive after their more stringent PCA control.

A Definitive Haplotype Map of the Asian Population

Kukita et al., page 918

Copy-number variants (CNVs) are recognized to be a significant source of variation in the human genome, and in the

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continuing search for variants that increase the risk of developing disease, a selection of CNVs that significantly contribute to susceptibility has been identified. A fundamental part of attributing disease risk to CNVs is that CNVs can be efficiently identified and that the CNVs found to be polymorphic in a population are documented. For these reasons, SNP data in which the genotypes of single markers have been converted into predictions of gains or losses of genomic regions have been utilized. Such analysis is often complicated by the diploid and heterozygous character of the human genome; the phase of the SNP data must be inferred so that the nature of the CNVs can be inferred. Complete hydatidiform moles (CHMs) are a DNA source that can bypass this issue. CHMs are products of conception in which all the genomic DNA is contributed by a single parent. This presents the situation in which the tissue can be homozygous across the genome. In this issue, Kukita and colleagues present their characterization of the CNV structure of CHMs from the Japanese population. Their data are collected to produce a definitive map of the SNP and CNV haplotypes of these samples.

HPSE2 Mutations Cause UFS

Pang et al., page 957; Daly et al., page 963

Ochoa syndrome, named after a referring physician, was later given the name urofacial syndrome (UFS), a much more descriptive title. As the current name implies, patients with this autosomal-recessive disorder have both urinary and facial phenotypes. Although it is the peculiar facial expression, an inverted smile, that most often brings these patients to the clinic, it is the dysfunctional urinary voiding that presents a potentially dangerous health issue. The failure to properly void urine can lead to urinary-tract infections and ultimately to renal damage and failure, making identification and treatment of UFS patients critically important. In this issue, two groups of researchers bring the field closer to identifying the molecular pathway involved in USF as they both report mutations in the same gene responsible for some cases of this disease. Using homozygosity mapping and sequence analysis, Pang and colleagues and Daly and colleagues independently identify *HPSE2* mutations in a number of ethnically diverse UFS patients. Although it was identified in 2000, not much is known about the function of heparanase 2, encoded by *HPSE2*. However, because *HPSE2* does share homology with a glycosyl hydrolase motif in *HPSE1* (a known heparatinase), it is likely to have a role in extracellular matrix structure and function, including cell signaling. The identification of *HPSE2* mutations in UFS patients will shed light not only on this disease but also on the function of this intriguing protein. Because *HPSE2* mutations do not account for all UFS cases, it will be interesting to discover what other genes are involved.