This month in *The Journal*

Robin E. Williamson[1]

The Many Steps to Becoming a Man

Flück et al., page 201

Male sexual development is an active process that involves a series of enzymes in the biosynthesis of androgens and ultimately ends with the creation of dihydrotestosterone (DHT), the steroid that is critical for the proper development of male external genitalia. In humans, there is a classic pathway of androgen biosynthesis that is well delineated, but although mutations in many of the classic components have been identified, there remain individuals who have disordered sexual development and who do not have mutations in those enzymes. In this issue, Flück and colleagues studied two families of such individuals in an effort to identify new players in the process of male sexual development. The authors focus on the AKR1C family of enzymes involved in a secondary pathway for the production of DHT. In one family, the authors find that the affected individuals who are XY but undervirilized and considered female have two mutations in *AKR1C2*. Determining what is happening with the individuals who are heterozygous for a mutation in *AKR1C2* is a bit more complicated. One such heterozygote is normal and fertile, whereas the other is severely affected. The authors discover that some individuals in the family also have a splicing mutation in *ARK1C4* that renders the encoded protein catalytically inactive and is likely responsible for this discrepancy. The affected heterozygote has this *ARK1C4* mutation in addition to an *ARK1C2* mutation, evidence that oligogenic inheritance might be to blame. In the second family, the authors determine that affected individuals have an aberrant fusion of *AKR1C1* and *AKR1C2* on one allele and a point mutation in *AKR1C2* on the other allele. The combination of discoveries in these families demonstrates the importance of the alternative DHT synthesis pathway in male sexual development.

Filter by Binding

Özgül et al., page 253

Retinal degeneration is a genetically heterogeneous phenotype: Mutations that can cause the disease have already been identified in over 200 genes, but about half of individuals who suffer from retinal degeneration do not have a mutation in any of these known genes. Such heterogeneity can make diagnosis and screening difficult. Exome sequencing is certainly contributing to the identification of causative mutations in Mendelian disorders, but the huge number of variants that result from such analyses needs to be filtered effectively to be useful. In this issue, Özgül and colleagues demonstrate the utility of using biological evidence to narrow the list of candidate variants. The focus of their efforts is the transcription factor CRX. CRX is involved in the regulation of photoreceptor genes, and the regulatory regions of many of the genes known to be mutated in retinal degeneration have CRX-binding sites. In previous work, the authors used chromatin immunoprecipitation to create a list of genes in the mouse genome that contain a Crx-binding site. The authors predict that the human orthologs of these genes are strong candidates for being mutated in individuals with retinal degeneration. Using this technique, the authors identify mutations in *MAK* in several of the individuals they study.

Combining to See an Effect

Tzeng et al., page 277

Because the amount of genotype information out there is constantly growing, the effort to develop the methodology to best assess the relationship between genetic variation and phenotypes is ongoing. The attention these days has shifted away from the examination of the main effects of single SNPs because it is increasingly recognized that such effects cannot explain a lot of the heritability of traits and complex diseases. Marker-set analyses have been a focus because of their ability to combine the signals of weak effects, decrease a heavy multiple-testing burden, and potentially generate uniformity across data from populations with different LD structures. There is now a repertoire of different approaches for how best to handle these types of analyses; each approach has advantages and limitations. In this issue, Tzeng and colleagues present their spin on things, and it includes the incorporation of gene-environment interaction effects. The authors demonstrate how their test can effectively handle both uncommon and common variants with opposite direction effects, and they compare their approach to other currently used methodologies to highlight how different scenarios affect performance. With an application to genotyping data collected to identify genetic variation that is

[1]Deputy Editor, *AJHG*
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associated with homocysteine levels, Tzeng et al. use their methodology to examine whether age is a modifying factor of genetic effects.

I've Got You under My Finger…or Not

Nousbeck et al., page 302

We usually think of fingerprints in terms of their use in forensics: The unique character of each person's fingerprints serves as a useful means of identification whether it be for security purposes or for reliably connecting a suspect with fingerprint evidence left at a crime scene. But, why did we evolve to have fingerprints, and what are the biological processes involved in their creation? Insight into addressing these questions can be provided by studying a group of individuals who do not have fingerprints. This condition, known as adermatoglyphia, can be isolated or accompanied by additional syndromic features. In this issue, Nousbeck and colleagues report that a mutation in *SMARCAD1* causes adermatoglyphia in the affected individuals of a large Swiss family. This finding originally eludes the authors because the major *SMARCAD1* transcript is not affected by the mutation. The authors search for additional transcripts in the linkage region and identify a shorter rare *SMARCAD1* transcript that has a unique 5′ exon and that is affected by a splicing mutation. Of particular note, this shorter transcript is primarily expressed in skin fibroblasts. The protein product of the large *SMARCAD1* isoform is predicted to function as a regulator of transcription, but the short isoform has not been previously studied. The authors suggest that the short isoform could be involved in the regulation of skin-specific factors that control the development of those little ridges on our finger tips.

The Eyes Have It

Larsson et al., page 334

When you look into the eyes of a loved one, do you see his or her soul? Do you feel the connection of your spirits? Do you take note of the crypt frequency in the iris or remark upon a peripupillary pigmented ring? In this issue, Larsson and colleagues report that these last two features, at least, are influenced by genetics. The authors perform a genome-wide association study for four iris characteristics: crypt frequency, which is a measure of how many spots of hypoplasia are visible around the iris; peripupillary pigmented ring, which is a hazel-colored ring of melanin deposited around the pupil; furrow contractions, which are indications of the thickness of the iris and develop where the iris folds in response to light; and the number of melanin accumulations, called iris nevi. Previous work has been very successful in identifying variants associated with eye color—so much so that a combination of just a handful of SNPs can be used to predict eye color with a high degree of accuracy—and here the authors hope to go a step further and learn about other aspects of the eye. These features are interesting traits to examine, and it is likely that, because of the connection between the development of the iris and the brain, the pathways involved with the texture and pigment characteristics of the iris will also affect neurodevelopment.