This Month in *The Journal*

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The Short and Tall of Height

Lanktree et al., page 6

Anthropometry is the measurement of humans and is used to understand physical variation between people. Popularized in the late 1800s, the collection of biometric data began as a means to catch repeat criminals. By compiling lists of measurements such as height, cheek width, arm span, foot length, etc. of people convicted of a crime, police could catch the same crook again despite the use of an alias. Like many new technologies, anthropometry was soon used to discriminate different "races" and categorize criminals on the basis of physical characteristics rather than behavior. Today, human measurement is a standard practice in clinics around the world. Birth weight, body length (height), and foot size can all be plotted against standard curves to determine how one compares to the average. Such measurements are also important for the clothing, toy, and automobile industries, to name a few. In this issue, Lanktree and colleagues perform a search for genetic loci contributing to the variability of human height. Although height is certainly influenced by environment and nutrition, genetics is also a strong determinant of adult height. Like other complex traits, many different genetic factors are thought to combine to influence final height. By looking at nearly 50,000 different SNPs in more than 100,000 people, Lanktree and colleagues identify a number of rare variants associated with human height. They conclude that using SNP arrays with dense coverage will uncover variants associated with many more complex traits.

Radical Hearing-Loss Mutations

Ahmed et al., page 19

When we eat a meal, the mitochondria in our bodies kick into action. Nutrients become oxidized (typically meaning that electrons are lost), whereas other molecules become reduced (they pick up the extra electrons), reducing their oxidation state. These so-called redox reactions are crucial for metabolizing our food and keeping our bodies running properly. Within the mitochondria, the energy released from a redox reaction is used to make ATP, the energy unit of our cells. Although these processes are necessary, they also lead to a negative side effect: free radicals. Free radicals are known to damage cells and thought to be involved in the aging process. Much research is focused on improving the body's ability to rid itself of these free radicals. Methionine sulfoxide is one such free radical. Methionine is a common residue in proteins found in the food we consume. During metabolism, methionine becomes oxidized into methionine sulfoxide. However, methionine sulfoxide derivatives quickly become free radicals that can damage the cell. Fortunately, our bodies have a system for controlling this: methionine sulfoxide reductases (MSRs) change methionine sulfoxide back to methionine. Different MSRs perform this task in different tissues. MSRB3 contains isoforms that target methionine sulfoxide in mitochondria. In this issue, Ahmed and colleagues identify *MSRB3* mutations in eight families with autosomal-recessive nonsyndromic hearing loss linked to the *DFNB74* locus. This study conclusively defines mutations in *MSRB3* as causative of DNFB74 and highlights the role of mitochondria in hearing loss.

On a Scale from 0 to *PTEN*

Tan et al., page 42

PTEN hamartoma tumor syndrome (PHTS) refers to a collection of heterogeneous phenotypes that are caused by germline mutations in *PTEN*. Some individuals with *PTEN* mutations have clinical features that are classified as Cowden syndrome, but not all people with Cowden syndrome have *PTEN* mutations. Likewise, the pediatric syndrome Bannayan-Riley-Ruvalcaba can also be due to *PTEN* mutations but is similarly genetically heterogeneous. Some of the common features among these patients can include macrocephaly and cancers, as well as skin, neurologic, and gastrointestinal manifestations. Having such a mix of overlapping disease presentations can make diagnoses and genetic counseling complicated, and the ability to identify patients who are likely to carry *PTEN* mutations would be advantageous. Previous analyses of patients with and without *PTEN* mutations have led to the development of criteria that can be used to predict the genotype of patients, but there are some limitations to the current guidelines. In this issue, Tan et al. present a scoring system that they have established on the basis of the clinical genotype and phenotype data that they collected from a large data set of patients. They derive criteria for pediatric and adult cases and demonstrate how these lead to improved predictions of *PTEN*-mutation status over those made

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with the current guidelines. The authors also evaluate the correlation between disease score and the levels of proteins in the PTEN pathway.

Duplications and Fusions

Klopocki et al., page 70
Syntosis is the abnormal fusion of neighboring bones. It typically occurs during development and is sometimes associated with a syndrome. Bones are formed by two different processes in the body. The appendicular skeleton and portions of the axial skeleton form via endochondrial ossification. In this process, a cartilage template is replaced by ossified bone. The majority of the axial skeleton forms by another means, intramembraneous ossification, which lacks the cartilage template. Interestingly, syntoses can take place in skeletal elements, arising by either form of ossification. Craniosyntosis is an example of syntosis occurring during intramembranous ossification and results in the premature fusion of skull bones. Syndactyly, or the joining of digits, is an example of syntosis occurring during endochondrial ossification. Unlike craniosyntosis, syndactyly may not involve the bones themselves, but rather just the connective tissue surrounding the bones. If this is the case, the phenotype is called syndactyly type I. The genetics underlying syntoses have been as elusive as the biological processes leading to them. In this issue, Klopocki and colleagues identify duplications in a regulatory region of *IHH* leading to both craniosyntosis and syndactyly in three separate families. *IHH* encodes a morphogen known to play a role in endochondrial ossification osteoclast differentiation. Finding the specific role for this protein in cranial and digit development will aid in our understanding of the complex process of syntosis.

In Search of What Is Missing

Yang et al., page 76
Missing heritability is what everyone is looking for these days. If the genetic components of complex traits are as large as they are supposed to be, then why do the variants identified as being associated with the traits explain so little of the heritability? What hasn't been found yet? Are there lots of rare variants with large effects out there? Do a bunch of common variants have such small effects alone that they can't be detected with single-SNP techniques? Is it a mix of both, or is something altogether different going on? Yang and colleagues have developed a tool that will hopefully assist in figuring out the answers to these questions. Their method involves evaluating the combined effects of all the SNPs on the genotyping arrays for an association with a complex trait. By doing this, the authors bypass the problem of common SNPs having effect sizes that are too small to be measured in reasonably sized data sets. The authors are then able to estimate the variance explained by all autosomal SNPs and by SNPs on the X chromosome, as well as to measure genetic relatedness and inbreeding coefficients. In this issue, the authors discuss the incorporation of their methods into a software tool called Genome-wide Complex Trait Analysis, GCTA, and demonstrate the useful functions available.