This Month in *The Journal*

Kathryn D. Bungartz[1] and Robin E. Williamson[2]

G-proteins and Cognitive ability

Ruano et al., page 113

As it has become clear that most of the significant associations identified in typical association analyses are going to account for just a small proportion of the heritable risk for complex diseases and traits, researchers have sought other methods to identify genetic variants that contribute to risk. One approach has been to look at the combined effect of variants in multiple genes in an effort to increase power. Along this vein, pathway analyses in which SNPs in genes involved in biological pathways are assessed collectively have successfully identified disease associations. Ruano and colleagues add a different spin on this idea and group the variants from genes that share cellular functionality. The thought is that many pathways will be affected by a convergent set of functional proteins. The authors use such a process to identify variants that are associated with cognitive ability. After a more traditional single-SNP genome-wide association analysis does not yield any significantly associated loci, Ruano and colleagues look at variants from within functional groups of genes that are known to be expressed in synapses. They find that the group of SNPs from synaptic heterotrimeric G-proteins is associated with cognitive ability. None of these markers reaches a notable level of significance in the original single-SNP scan. The authors then go on to replicate the association between variants in heterotrimeric G-proteins and cognitive ability in an independent dataset.

Aggrecan and Osteochondritis Dissecans

Stattin et al., page 126

Proteoglycans (PGs) are glycoproteins that contain variable numbers of covalently attached glycosaminoglycan (GAG) chains. The type and length of GAG chain(s) attached provide temporal and spatial specificity to PGs. Aggrecan is probably the best known and most studied PG. As a lectin, aggrecan contains both a hyaluronan-binding domain and a C-type lectin domain. It is heavily glycosylated and contains distinct regions of keratin sulfate and chondroitin sulfate. Numerous glycosylated aggrecan proteins can be found attached to hyaluronic acid, comprising a water-retaining matrix that is crucial for cartilage function. Aggrecan interacts with other proteins found in cartilage, including tenascins and fibulins. Null and functional null mutations in *ACAN*, the gene encoding aggrecan, have been shown to result in a variety of skeletal diseases, including spondyloepiphyseal dysplasia type Kimberley (see Am. J. Hum. Gen. *77*, 484–490) and SEMD aggrecan type (see Am. J. Hum .Gen. *84,* 72–79). Here, Stattin and colleagues search for the gene responsible for familial osteochronditis dissecans in a large Swedish family. Osteochondritis dissecans is a rare skeletal disorder characterized by separation of cartilage and subchondral bone from the surrounding tissue. The authors utilize genome-wide linkage analysis to limit the disease-associated haplotype to a region including *ACAN*. Sequencing this gene reveals a causative mutation in all affected subjects. The authors use further biochemical analyses to determine the mutation's detrimental effects, which include altered binding to other cartilage extracellular matrix proteins. This study emphasizes the important role of aggrecan in skeletal development and maintenance.

GRXCR1 and *Grxcr1* Mutations Cause DFNB25 and the Pirouette Mouse Phenotype, Respectively

Schraders et al., page 138; Odeh et al., page 148

Hearing impairment can be associated with a disease (syndromic), but it is often found on its own (nonsyndromic). Nonsyndromic forms of hearing loss, or deafness, can be autosomal dominant (DFNA), autosomal recessive (DFNB), or X-linked (DFN). The number following the letter designation represents the order in which the hearing-impairment locus is described. Thus, DFNB25 is the 25th locus described to be associated with autosomal-recessive hearing impairment. Although numerous DFNB loci have been identified, causative genes have only been reported for about half of the loci described. In this issue, Schraders and colleagues use homozygosity mapping to narrow the DNFB25 locus. The homozygous region found to be shared by ten Pakistani families, one Dutch family, and one isolated Dutch case of hearing impairment contains the complete coding region of *GRXCR1*. In this same issue, Odeh and colleagues find mutations in *Grxcr1* to be responsible for the pirouette mouse phenotype. Here, five independent strains of mice exhibiting deafness and circling behavior (a sign of vestibular dysfunction) are found to have loss-of-function mutations in this gene, and these mutations result in abnormally thin and slightly shortened hair cell sterocilia within the inner ear. Likewise,

[1]Science Editor, *AJHG*; [2]Deputy Editor, *AJHG*
DOI 10.1016/j.ajhg.2010.01.018.

when Schraders et al. sequenced *GRXCR1* in the families they studied, they found pathogenic mutations in both the Dutch family and the isolated case as well as in two of the Pakistani families. Both groups find *GRXCR1* and *Grxcr1* to be preferentially expressed in the cochlea. A potential function of GRXCR1 is predicted to be actin cytoskeletal remodeling.

Distribution and Most Recent Common Ancestor of 17q21 Inversion

Donnelly et al., page 161

A region of complete linkage disequilibrium on 17q21 has been found to harbor an inversion of about 900 kb. The most common version of the chromosome is called H1, and the inverted orientation of the chromosome is called H2. Association studies have focused on the region because of its potential relationship with neurodegenerative disorders, but there is an increasing interest in determining where and when the inversion arose. Previous estimates have suggested that the inversion occurred 2–3 million years ago, but there has been controversy about that timeline. Here, Donnelly and colleagues collect data from populations from around the world and combine it with previously published datasets and data from nonhuman primates to further examine this matter. Their work in nonhuman primates suggests that the inversion did occur on an ancestral background or that the inverted version was in fact the ancestral orientation of the chromosome, but analysis of their human data leads them to a more complicated conclusion. The authors provide evidence that suggests that, although the H2 orientation is ancestral in nonhuman primates, the H1 version is ancestral in humans. They hypothesize that an early inversion on the nonhuman primate H2 background rose to fixation in humans and became the common H1. It was on this H1 background that the inversion then occurred again to create the human H2 chromosomes observed today. The authors also conclude that the human inversion was most likely to have originated either in Africa or in Southwest Asia. These different insights into the evolutionary history of the region lead the authors to suggest that the human inversion occurred as recently as 16,400–104,400 years ago.

Association Tests in Structured Samples

Thornton and McPeek, page 172

Population structure and the incorporation of related samples can create problems for association studies. In case-control analyses, false positives can result from hidden structure, and correction methods cannot always handle all types of data, particularly if related individuals are included. Family-based methods are robust to population structure, but they often lack power and require additional data that can be difficult to obtain. Thornton and McPeek address these issues with the introduction of ROADTRIPS, a method that can perform genome-wide association analyses on case-control samples in the presence of both population and pedigree structure. In order to compare ROADTRIPS to other methods, the authors first generate a number of simulated datasets in which different combinations of population structure and relationships are set. As expected, ROADTRIPS has better type-1 error than algorithms that are not able to correct for both population and pedigree structure. ROADTRIPS also performs well when limited population structure is provided as well as in the presence of different rates of missing genotype data. The authors illustrate their method on data from association analyses for rheumatoid arthritis and alcoholism. These real-data examples demonstrate the ability of ROADTRIPS to handle scenarios in which the relationship status of samples is incorrectly labeled, hidden population structure is present, and missing genotype data is variable.