This Month in *The Journal*

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Diabetic-Nephropathy Susceptibility

He et al., page 5

Type I diabetes mellitus (T1DM) results from the body's inability to produce sufficient insulin and is typically diagnosed in children (juvenile diabetes). Diabetes results in high levels of blood sugar, which may lead to capillary damage. Retinopathy and kidney damage (nephropathy) are among the potential complications of T1DM. Although diabetic nephropathy (DN) is the primary cause of death in T1DM patients, only about 30% of T1DM patients develop this condition. There is evidence of a genetic component to the development of DN in T1DM; however, the complication does not follow simple Mendelian rules of inheritance. He and colleagues use a multistage association study of a region of chromosome 3q22 previously linked with DN in T1DM patients to identify genetic factors that might influence the occurrence of this condition. Finish, Icelandic, and British patients with T1DM are divided into two groups: those with no clinical sign of renal damage (1874 patients) and those with end-stage renal disease (ESRD), determined by persistent large amounts of albumine in the urine (macroalbuminuria) and retinopathy (1822 patients). Initial screening identifies 27 associated SNPs in one Finish cohort. Replication in the other populations finds significant association of the minor allele C of SNP rs1866813 with DN (odds ratio = 1.33). Although haplotype-block analysis reveals no stronger association, the intergenic region containing rs1866813 is evolutionarily conserved. These data suggest that rs1866813 might influence one or a number of neighboring genes expressed in the glomerulus of the kidney, including *NCKI* and *TMEM22*.

Genome-wide Association in Alzheimer Disease

Beecham et al., page 35

Alzheimer Disease (AD) is a debilitating disorder characterized by dementia in older individuals. Although there is evidence that genetic factors are involved in the development of late-onset Alzheimer Disease (LOAD), researchers have had a difficult time identifying variants that contribute to disease risk. Risk alleles in one gene, *APOE*, have been consistently found to be strongly associated with LOAD susceptibility, and the strength of the effect of variants at this locus is strong enough to be picked up with the use of linkage techniques. Other loci with such large effects have not been found. Beecham et al. hope to identify additional genetic factors that contribute to LOAD risk by executing a large case-control genome-wide association study. In the genome-wide analysis, one non-*APOE* SNP on 12q13, rs11610206, is associated with LOAD at a genome-wide level of significance. This SNP, which lies within a region previously linked to AD, is also found to be significantly associated in a replication analysis of an independent data set of cases and controls. The authors then use imputation to compare and combine the association results from their study with those from another genome-wide analysis. Beecham et al. hope that future work will establish the mechanism behind the relationship between the associated loci and LOAD risk.

GWAS for Mean Platelet Volume

Meisinger et al., page 66

The number of platelets circulating in the blood needs to be carefully maintained to ensure a proper balance between the body's ability to effectively respond to damage and an abnormally high level of clot formation that can cause strokes or heart attacks. Although some of the factors involved in this tight regulation are known, much of the process remains to be elucidated, but there is evidence that mean platelet volume (MPV) is under genetic control. MPV is an important diagnostic measure, because it can serve as an indicator for how well patients will respond after a cardiovascular or cerebral event. Meisinger et al. report the results of their genome-wide association study, in which they work to establish genetic variants that are associated with MPV. Their initial analysis is performed in a large German group. Significant associations are then examined further in three independent replication data sets; one UK data set and two German data sets. Of the three significant associations that were identified and replicated, a SNP in *WDR66* is believed to have the strongest effect. The authors follow up this result by performing a denser search and identify additional *WDR66* variants that are associated with MPV in their samples.

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ACAN Mutation in SEMD Aggrecan Type

Tompson et al., page 72

Spondylepimetaphyseal dysplasia (SEMD) encompasses a group of skeletal disorders characterized by short stature due to defective remodeling of the vertebra (spondyl) and long bones, including both the epiphyses and the metaphyses. Several different genetic mutations leading to alternative forms of SEMD have been identified in genes encoding extracellular-matrix or matrix-remodeling proteins found in cartilage. Aggrecan is the most abundant proteoglycan of cartilage extracellular matrix, and recent genome-wide studies have implicated *ACAN* as a regulator of height. Additionally, a mild dominant form of SEMD, termed SEMD Kimberly type, was previously shown to be caused by a frameshift mutation in *ACAN*. Here, the authors identify a new form of SEMD characterized by extreme short stature and unique radiographic findings, including clefts of the cervical vertebral bodies and extra ossification centers in bones of the hands. Through homozygosity mapping, Tompson et al. identify a candidate region containing 193 annotated genes. Using expression analysis, they narrow the number of genes to only those expressed in cartilage and subsequently identify a point mutation in *ACAN* changing a conserved aspartic-acid residue. In addition to altering a conserved amino acid, the homozygous recessive mutation might create an additional glycosylation site on the protein, altering its biological activity. Carrier parents and siblings present with shorter stature than the sibling lacking the mutation. The authors term this new autosomal-recessive disease "SEMD aggrecan type" and suggest the possibility of a carrier phenotype.

FIG4 Mutations in ALS

Chow et al., page 85

Previous work in human and mouse has demonstrated that disruption of *FIG4* affects motor-neuron function. The mouse model for deficiency of this phosphoinositide 5-phosphatase presents with severe neuron degeneration, and *FIG4* mutations have been identified in a severe form of Charcot-Marie-Tooth disease, CMT4J. Here, Chow et al. predict that some cases of amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) might also be caused by mutations in *FIG4*. ALS and PLS are neurodegenerative diseases, of which little is known about the genetic etiology. Only a small percentage of the genetic etiology of ALS has been determined, and no mutations have yet been linked to PLS. To determine the role that disruption of *FIG4* might play in ALS and PLS, the authors screen a large patient data set consisting of both familial and sporadic cases. A variety of variants are identified, including truncation mutations, splice-site mutations and missense mutations. The pathogenicity of the missense alleles is tested through the use of a yeast rescue assay, and the authors establish that two of the missense mutations are likely to be disease causing. The authors suggest that it is the involvement of phosphoinositides in vesicle trafficking that is affected. Disruption of phosphoinositides has been linked to other motor-neuron disorders, and the vesicle-trafficking process is thought to be important in these diseases because of the high level of membrane turnover in motor neurons.