This Month in *The Journal*

Robin E. Williamson[1]

Rare *ATM* Variants and Breast Cancer

Tavtigian et al., page 427

Homozygous mutations in *ATM* cause the autosomal-recessive disorder ataxia-telangiectasia, but for many years there has been debate over whether heterozygous variants in *ATM* increase the risk of developing breast cancer. Researchers began to suspect that the disease-causing alleles might have an additional monoallelic effect after reports of the increased prevalence of breast cancer in the families of patients with ataxia-telangeictasia. Unfortunately, results of association studies looking for risk variants have been conflicting. Several recent large-scale studies have added support to the hypothesis that *ATM* variants, more specifically those mutations that cause ataxia-telangiectasia, do in fact also increase risk of breast cancer. In this issue, Tavtigian and his colleagues perform an analysis on several breast cancer data sets to further delineate the risk conferred by *ATM* sequence substitutions. By analyzing data from a large number of cases, the authors are able to identify enough variants so that they can analyze separately the effects of truncating mutations versus rare missense mutations. Truncating mutations are expected to be deleterious and have an effect, and that is seen here, but things are more complicated when the effects of rare missense alleles are assessed. By using their method of grading each variant on the basis of its predicted deleterious effect to the gene, the authors are able to make pools of rare missense alleles. They find evidence that, as the variant is deemed more deleterious, it is also associated with a larger risk effect. Additional analysis examines these missense variants in specific regions of the gene, and the authors are able to suggest that sequence substitutions in certain domains have a greater effect than others.

Clinical Diagnostics in Human Genetics

Kohler et al., page 457

Without the ability to make a proper diagnosis for a sick patient, clinicians can have significant difficulty in recommending appropriate treatment, predicting disease prognosis, or providing constructive genetic counseling. Unfortunately, the tremendous number of disease possibilities, along with the overlap of phenotypes in and the rarity of many of them, makes it impossible for physicians to always recognize a disease on the basis of their experience alone. For aiding in the clinical diagnositic process, phenotypic data have been compiled into searchable databases that allow users to input the features of a patient and generate a list of possible candidate diagnoses. Although such lists surely assist clinicians and their patients, Kohler and colleagues suggest that additional advancements to the process could improve the utility of the output. Here, the authors report on their development of a statistical model implemented in a web application named the Phenomizer that works with the terms included in the human phenotype ontology to produce a ranked list of candidate diagnoses and assign each with a significance score. If the phenotypic input is not specific enough to generate a list of significant differential diagnoses, the physician then learns that more specific details about the patient's condition need to be collected. This will potentially contribute to tailored follow-up and specialist recommendations that will focus on distinguishing one group of syndromes from another.

Familial Hemophagocytic Lymphohistiocytosis Due to Mutations in *STXBP2*

zur Stadt et al., page 482

Hemophagocytic lymphohistiocytosis (HLH) is a severe syndrome in which the immune system is highly dysregulated, resulting in the eventual loss of immune homeostasis. HLH patients are affected by fever, hepatosplenomegaly, and cytopenia, and the condition is often fatal if proper immunosuppressive treatment is not administered. Genetic studies of the familial form of the disorder (FHL) have identified mutations in *PRF1*, *UNC13D*, and *STX11* that are responsible for the disease in a percentage of inherited cases, but a great deal of genetic heterogeneity has been observed and a number of cases remain in which no mutations have been found. In an effort to learn more about the genes that are dysfunctional in FHL, zur Stadt and colleagues perform homozygosity mapping in FHL patients who do not have any mutations in the known genes. Their inspection of the genes in a locus on 19p reveals a number of mutations in *STXBP2* that encode the syntaxin binding protein 2. The missense mutations are shown to affect protein stabilization and also disrupt the interaction between STXBP2 and STX11. Although the function of STXBP2 is not yet well understood, its

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colocalization and relationship with STX11 in hematopoietic cells suggests that the two proteins work together in the process of granule exocytosis.

IREB2 Variants in Chronic Obstructive Pulmonary Disease

De Meo et al., page 493

Although genome-wide methods have been successful in identifying a number of genetic variants associated with complex disease, the cost of correcting for the large number of tests involved with evaluating so many markers can decrease a study's ability to observe significant associations. One way to minimize the need for a large correction is to limit the number of markers tested by focusing in on regions or genes that are most likely to be involved in disease pathogenesis. De Meo and colleagues use such a strategy here in their research to identify risk alleles for chronic obstructive pulmonary disease (COPD). A number of studies have identified variants with significant effects, but results have not always replicated. Here, the authors reduce the number of markers they analyze by first examining which genes are differentially expressed in patients and controls. Their analysis pinpoints a significant association between variants in *IREB2* and the risk of developing COPD. *IREB2* expression is higher in patients than in controls and the protein localizes to a number of structures within lung tissue. Of note, *IREB2* SNPs have also been associated with lung cancer risk. The authors suggest that *IREB2*'s role in iron metabolism is a factor in COPD development on the basis of previous work that suggests a relationship between the distribution of lung iron and inflammation.

Incidence of Fragile X Syndrome

Coffee et al., page 503

Once the trinucleotide repeat expansion in the 5′ UTR of *FMR1* surpasses a certain length, it causes Fragile X syndrome (FXS) via hypermethylation and gene silencing. Traditionally, researchers determine whether an individual has such a long repeat expansion, termed a full mutation, through Southern blot and PCR techniques. These methods are costly and cumbersome and do not always yield reliable results, so using them for high-throughput assessment of a large number of samples has not been a reasonable possibility. In this issue, Coffee and colleagues report their development of a FXS-screening method that capitalizes on the fact that the *FMR1* promoter is differentially methylated in those with the full mutation versus those without. Specifically, male FXS patients with a full expansion mutation have a high level of *FMR1* methylation and unaffected males have no methylation. Similarly, female carriers of a full mutation have a high ratio of methylated versus unmethylated *FMR1*. The authors validate their strategy on a set of male samples and demonstrate that they are able to detect the full-mutation carriers with 100% sensitivity and 100% specificity. With such an effective and low-cost screening tool, the authors are able to analyze over 36,000 newborn blood samples to make an unbiased estimate of the incidence of FXS in the general population.