This Month in Genetics

Kathryn B. Garber[1,*]

NF1-like Syndrome Really Isn't Much Like NF1

Diagnosis of neurofibromatosis type 1 (NF1) is made clinically through the use of a well-established set of diagnostic criteria. Two of the key features included in these criteria are the presence of more than five café-au-lait macules and of axillary or inguinal freckling. The more serious features of this syndrome include neurofibromas and bone lesions. Legius syndrome (formerly known as NF1-like syndrome) is due to mutations in *SPRED1* and overlaps clinically with NF1 in that affected individuals also commonly have multiple café-au-lait macules as well as inguinal and axillary freckling. To better understand the full phenotypic spectrum of Legius syndrome, Messiaen et al. used a two-pronged approach to collect the largest set of *SPRED1* mutation-positive individuals to date. They used data from their clinical testing lab on patients referred for *SPRED1* mutation testing, as well as a set of more than 1300 anonymous samples from individuals with features of NF1 but no detectable *NF1* mutation. Their data show that many people with Legius syndrome could be erroneously given a diagnosis of NF1. In the first component of the study, nearly half of their *SPRED1* mutation-positive individuals met the clinical criteria for NF1, although they did not, in fact, have the disease. The importance of distinguishing these related diseases is that the severity of Legius syndrome appears to be much lower than that of NF1; none of the individuals who had mutations in *SPRED1* had neurofibromas, osseous lesions, or a symptomatic optic pathway glioma. Thus, the authors recommend that *SPRED1* mutation testing is an important consideration in *NF1* mutation-negative individuals who have café-au-lait spots with or without freckling but who lack other NF1 diagnostic features.

Messiaen et al. (2009) Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. JAMA 302, 2111–2118.

Five Years of Data on ERT for Fabry Disease

Fabry disease is a lysosomal-storage disorder whose key morbidity and mortality result from renal and cardiac disease. Enzyme replacement therapy (ERT) became available in the early 2000s and has proven to be effective in randomized controlled trials. Now, some of the first long-term data on ERT are becoming available. Mehta et al. report five years of observational data on agalsidase alfa for Fabry disease, which were collected as part of a multinational registry, the Fabry Outcome Survey. Baseline and five-year data were available for 181 adults in this registry. Treatment with agalsidase alpha over five years had positive effects on Fabry disease progression. ERT led to sustained reductions in left ventricular mass and increased cardiac contractility in patients who had cardiac hypertrophy at baseline, as well as stable measurements of both in those without baseline hypertrophy. The treatment slowed the decline of glomerular filtration rates as compared to what is expected for the natural course of disease, and it was associated with reduced pain and increased quality of life. Although there are inherent limitations to large, observational studies such as this one, these data provide additional evidence for the long-term safety and efficacy of agalsidase alfa for treatment of Fabry disease.

Mehta et al. (2009) Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: An analysis of registry data. Lancet. Published online December 2, 2009. 10.1016/S0140-6736(09)61494-8.

Separating the Haves from the Have-Nots

When bone marrow transplants are performed, attempts are made to match the donors with the recipients to ensure histocompatibility between the two. Even with HLA-identical siblings, however, the risk of graft-versus-host disease (GVHD) is still quite high. McCarroll et al. noticed that surveys of copy-number variation (CNV) have revealed whole-gene deletions that can be quite common in a population, and they wondered: Could these be the key to GVHD? If a bone marrow donor does not express a protein because he is homozygous for a deletion CNV, whereas the recipient expresses the protein, would the engrafted bone marrow recognize the protein as foreign and generate a GVHD response? To explore this hypothesis, they selected a set of six common deletion alleles that are expressed in the tissues relevant to acute GVHD, and they genotyped these deletions in a set of bone marrow transplantation donor-recipient pairs. Donor-recipient mismatch for a deletion encompassing *UGT2B17* was associated with risk for GVHD, a finding that was replicated in additional samples. In further support of the role of *UGT2B17* in GVHD, T cells and sera from some patients with GVHD recognized peptides from the encoded protein. Although the odds ratio of GVHD associated with mismatch at *UGT2B17* is 2.5, the rate of sibling mismatch at this locus will be less than 10%, so this locus can explain only a small fraction of GVHD. However, this paradigm could hold true at other

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
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loci, and it is plausible that, when considered together, CNV could have a large impact on GVHD.

McCarroll et al. (2009) Donor-recipient mismatch for common gene deletion polymorphisms in graft-versus-host disease Nature Genetics I, 1341–1345.

A Nod to Autophagy

Variation in *NOD2* and *ATG16L1* are each associated with risk of Crohn disease, an inflammatory disease of the gut. *NOD2* is a pattern-recognition receptor that helps the body recognize foreign invaders, whereas *ATG16L1* encodes a protein that is involved in autophagy. Cooney et al. identify a previously unknown link between the two processes that helps explain how these seemingly disparate pathways can both influence Crohn's disease. They show that the bacterial ligand of NOD2, muramyldipeptide, can stimulate autophagy in dendritic cells, and this process influences MHC class II antigen presentation by these cells. Dendritic cells from individuals who carry variation in *NOD2* or in *ATG16L1* that is associated with Crohn disease show defects in both of these processes, as well as a reduced ability to control intracellular bacterial infections. This connects two strong genetic risk factors for Crohn disease into a single pathway and further specifies the connection between Crohn disease and aberrant inflammatory responses.

Cooney et al. (2009) NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. Nature Medicine. Published online December 6, 2009. 10.1038/nm.2069.

Molecular Mechanism for Alpha2A-Adrenergic Receptor in Type 2 Diabetes

Genome-wide association studies are all the rage, and they have produced some very exciting results over the past few years. However, we shouldn't forget the very powerful role that model systems can play in identifying candidate genes for complex traits. This was the approach taken by Rosengren et al, who studied a well-characterized animal model of type 2 diabetes (T2D), the GK rat. They used congenic strains with varying amounts of the GK-derived major diabetes susceptibility locus to identify a T2D candidate gene that opened the door to understanding a molecular pathway involved in T2D. They found that overexpression of the alpha2A-adrenergic receptor (alpha[2A]AR) in GK rats was associated with reduced β cell exocytosis as a result of impaired insulin granule docking at the plasma membrane. This gene is conserved, and the researchers found that a similar mechanism holds true in people. They identified a SNP in *ADRA2A* that was associated with impaired insulin secretion in humans because of hyperactive signaling through alpha(2A)AR. The same SNP was also associated with T2D in a case-control sample. Previous studies have implicated alpha(2A)AR in control of blood pressure and in adipocyte function. Because heart disease, diabetes, and stroke are all parts of the metabolic syndrome seen in overweight individuals, this receptor could be part of a central pathway relevant to this disorder.

Rosengren et al. (2009) Overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes. Science Express. Published online November 19, 2009. 10.1126/science.1176827.

This Month in Our Sister Journals

Mutational Analysis of *EDNRB* and *EDN3* in Hirschsprung Disease

Hirschsprung disease (HSCR) is a developmental defect in which the intestinal tract is not completely innervated. Although it can be inherited as part of a syndrome—for example, there is a 100-fold increased risk of HSCR associated with Down syndrome—sporadic, nonsyndromic HSCR also occurs. Two signaling pathways involved in the development of the enteric nervous system are known to play roles in HSCR: the RET signaling pathway and the endothelin-3 (EDN3)/endothelin receptor B (EDNRB) pathway. Sanchez-Mejias et al. were interested in further defining the role of genetic variation in *EDN3* and *EDNRB* in the development of HSCR. They screened both genes in 196 people with HSCR and identified variants in both genes. These variants included a nonsense mutation in an exon 5′ to the previously defined exon 1 in *EDNRB*. This is the first suggestion that this upstream exon might be important for HSCR and should be considered further in additional studies. They also find evidence that a specific *EDN3* haplotype is overrepresented in their case sample, and they argue that variations in this gene could be common, low penetrance contributors to risk of HSCR. Some of the patients studied carried more than one HSCR-risk allele. It remains to be seen how this variation combines to influence the development of the enteric nervous system.

Sanchez-Mejias et al. (2009) New roles of EDNRB and EDN3 in the pathogenesis of Hirschsprung disease. Genetics in Medicine. Published online December 8, 2009. 10.1097/GIM.0b013e3181c371b0.

How Many Genes for Stripes and Spots?

How does a tiger get its stripes? It's a question that my four-year old has asked me, but the truth is that we really don't know the answer. We've gotten a bit closer with the work of Eizirik et al., who used domestic cats to understand the genetics of mammlian coat patterning. Breeding lore suggested that four basic coat patterns in cats are the result of four alleles of a single locus, *Tabby*. Eizirik et al. performed systematic breeding of cats with these four patterns and

found evidence that there are actually three loci that work in combination to determine coat patterning. On the basis of the patterns that they have seen in these cats, the authors propose that coat patterning involves two processes: one in which the spatial patterns are laid down, then one in which pigmentation patterns are established via the spatial patterns. Now, who wants to go breed tigers to see whether the same thing holds true in that species? Any takers?

Eizirik et al. (2009) Defining and mapping mammalian coat pattern genes: Multiple genomic regions implicated in domestic cat stripes and spots. Genetics. Published online October 26, 2009. 10.1534/genetics.109.109629.