This Month in *The Journal*

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

Agrin Congenital Myasthenia

Huze et al., page 155

Myasthenia, or muscle weakness, is a primary component of many congenital disorders. This weakness is widely attributed to defects in the transmission of signals from the nerve to the skeletal muscle and can be categorized on the basis of the location of the defect. For example, myasthenia can be caused by presynaptic, synaptic, or postsynaptic neuromuscular defects. Mutations in many genes encoding synaptic receptors, ion channels, and membrane structural proteins are known to be responsible for congenital myasthenic syndromes (CMS); however, no mutations have been reported in neural secreted factors. To date, the underlying genetic defect in numerous CMS patients has remained elusive. Here, Huze and colleagues identify a homozygous missense mutation in *AGRN* in a family with CMS. The mutation is inherited in an autosomal-recessive manner. *AGRN* encodes the heparan sulfate proteoglycan agrin, of which specific splice forms localize to the neuromuscular junction (NMJ). Neural agrin has been shown to be important for acetacholine receptor (AChr) clustering in model systems. Here, the authors find that although neural agrin localizes to NMJs in their patient, NMJ organization is abnormal. Surprisingly, AChR clustering is found to be normal, as is α-dystroglycan binding. Several different functional studies carried out in this study corroborate these findings. Together, these data indicate a previously undescribed role of agrin in NMJ maintenance and add *AGRN* to the growing list of CMS-causative genes.

Skewed X Chromosome Inactivation and Trisomy

Warburton et al., page 179

During embryogenesis, X chromosome inactivation (XCI) generally occurs randomly, such that approximately 50% of cells contain an inactive maternal copy of the X chromosome and 50% of cells contain an inactive paternal copy. There are situations in which the ratio of cells with maternal copies to cells with paternal copies is skewed in one direction or the other. When this skewing is higher than 90%, the XCI is considered highly skewed (highly skewed X chromosome inactivation, or HSXI). In many studies, HSXI has been associated with increased rates of recurrent spontaneous abortions, but the reasons behind this relationship have not been completely elucidated, and inconsistent results have made it difficult to make solid conclusions. Although HSXI can occur at a small frequency as a result of chance, selection against an abnormal X chromosome is thought to play a role in many cases. A great deal of work in female carriers of X-linked diseases has demonstrated that skewing often results such that the abnormal X chromosome is inactive in a higher percentage of cells. It has therefore been hypothesized that the increased rate of recurrent spontaneous abortions seen in cases of HSXI may be due to the high loss of male conceptions that inherit the mutant X chromosome. However, it has been discovered that only a low percentage of lost male conceptions are chromosomally normal. In contrast, a large percentage of pregnancy losses are trisomic. The presence of an abnormal X chromosome has also been linked to a decrease in the size of the oocyte pool, which has been hypothesized to be at the root of the correlation between advanced maternal age and increased risk for trisomic conceptions. Warburton et al. predict that there is an underlying factor that causes both the HSXI and trisomy. Therefore, the authors sought to identify a correlation between HSXI and trisomic conceptions. After carefully controlled analyses, the authors conclude that there is no correlation between trisomy and HSXI.

Human Variation in Host Response

Ko et al., page 214

Genetic variation is critical to the evolution of a species because it provides the means for natural selection to take place. Alterations in the genetic code may make one more or less susceptible to a disease or infection and may thus be selected for or against over time. Variants in the human genome are currently under close scrutiny for association with a wide variety of complex diseases, including diabetes, heart disease, and schizophrenia. Another aspect of genetic variation is the potential of a variant to alter a response to a pathogen such as *Pneumocystis* or *Salmonellae*. However, unlike genome-wide association studies (GWAS) for common diseases, not many studies have yet identified genes associated with infection. In this issue, Ko et al. use an in vitro assay, which they devised, to screen for genes involved in bacterial infection. Using Hi-HOST, Ko and colleagues measure bacterial invasion, host cell death, and host cytokine production after infection of HapMap lymphoblastoid cells with *S. typhimurium*. Correlating their

[1]Science Editor, *AJHG*; [2]Deputy Editor, *AJHG*
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findings with GWAS data on these same cells, the authors find an association between a variant in *CARD8* and Salmonella-induced cell death. CARD8 modifies caspase-1, which the authors correlate with Salmonella-induced cell death, bringing the story full circle. Further investigation of the *CARD8* variant in different human and nonhuman populations reveals that this variant probably arose via adaptive evolution. Finally, the authors find the derived *CARD8* allele more often in patients with systemic inflammatory response syndrome (SIRS) than in healthy controls, implicating this variant in susceptibility to acute inflammatory disease as well.

X Chromosome Association with Progression to AIDS

Siddiqui et al., page 228

Acquired immunodeficiency syndrome, or AIDS, is a pandemic condition affecting people worldwide. Suffering from a syndrome caused by infection with human immunodeficiency virus (HIV), AIDS patients suffer from a failing immune system that often culminates in death due to opportunistic infection or cancer attributed to the depletion of CD4+ T helper lymphocytes. Genetic differences in *CCR5* have been shown to influence a person's susceptibility to HIV infection. Likewise, genetics may play a role in HIV progression to AIDS. In fact, studies have associated variants in the MHC locus with the viral load of HIV tolerated and with the rate of disease progression. These associations may differ as a result of ethnic (i.e., genetic) background. Rhesus macaques have long been used as animal models for HIV pathology and vaccine trials because they can become infected with the monkey HIV equivalent, simian immunodeficiency virus (SIV). However, little is known about genetic similarities of HIV and SIV infection and disease progression between macaques and humans. Here, Siddiqui and colleagues perform a genome-wide association study for AIDS-free survival of SIV-infected macaques and follow up their findings in humans. In addition to confirming the association of AIDS progression and MHC variants in the monkeys, this group identifies a variant on the X chromosome that is protective against AIDS disease progression. They confirm this finding in humans and find that the variant is more prevalent among Asian women than among European or African women, which probably provides this ethnic group with a selective advantage.

Correction of CNS Defects in MPSII Mice

Polito and Cosma, page 296

Deficiency of iduronate-2-sulfatase (IDS) causes mucopolysaccharidosis type II (MPSII), a disease characterized by deposits of glycosaminoglycans (GAGs) in a variety of tissues, leading to hepatosplenomegaly, cardiovascular disorders, skeletal features, retinal and hearing problems, and neurological deterioration. In concert with these phenotypes, affected individuals also excrete high levels of GAGs in their urine. The mouse model for MPSII shares many of the same features with people affected by MPSII and has served as an important resource for evaluation of various treatment options. Previous gene-therapy work with a vector carrying human IDS has successfully treated many aspects of the disease, but because the therapy cannot pass the blood-brain barrier (BBB), the neurological defects are difficult to treat with such methods. Here, Polito and Cosma modify the vector used, in an effort to establish a therapy that can cross the BBB to rescue the CNS effects of MPSII while also treating the effects to other organs. With a single injection of this new vector, the authors are able to correct all aspects of MPSII in the mouse model for more than 18 months. The authors demonstrate that the accumulation of GAGs in all tissues is ameliorated and that the level excreted in the urine also returns to normal. Additionally, signs of neurodegeneration are cleared and the mice show improvement in their gross motor skills. Importantly, the authors provide evidence that demonstrates that the correction of the CNS defects is most likely due to the established crossing of the therapy across the BBB.