This Month in Genetics

Kathryn B. Garber[1,*]

Gene-Expression Patterns Predict MS

People who develop multiple sclerosis (MS) first present with a clinically isolated syndrome (CIS), which is a single neurologic episode compatible with MS that is caused by inflammation and demyelination in the central nervous system. Although approximately one-third of people with CIS progress to diagnosable MS within a year, others never go on to have MS. The trick is figuring out who is at the most risk. Physicians use radiographic methods to make predictions, but these methods are not extremely accurate, so Corvol et al. explored molecular methods of risk stratification. In $CD4^+$ lymphocytes of people with CIS, they identified gene expression signatures that are characterized by downregulation of proinflammatory genes. Not only can the signatures be used to distinguish people newly diagnosed with CIS from controls, they also highlight a group of people with CIS who are at much higher risk of conversion to MS and at a faster rate than the rest of the CIS group. Beyond these risk predictions, this work could also help us understand how MS develops. One of the most striking changes in gene expression in the high-risk CIS group is the downregulation of *TOB1*, which encodes a repressor of T cell proliferation. Altered *TOB1* expression could be an early defect that is pivotal in the development of the devastating effects of this autoimmune disorder.

Corvol et al. PNAS. Published online August 8, 2008. 10.1073/pnas.0805065105

Exploring West Nile

Since its appearance in the United States in 1999 and subsequent spread, West Nile virus has become an infamous pathogen across the country. What many may not know is that serious disease occurs in less than 1% of people infected with the virus., and few factors governing susceptibility to West Nile infection and disease are known. Krishnan et al. approached this problem with a forward genetics screen using siRNAs from across the genome to study West Nile infection in cell culture. Among the host susceptibility factors are genes involved in intracellular protein trafficking, endoplasmic reticulum associated protein degradation, immunity, and the transport of ions and biomolecules, whereas the major factor involved in resistance to West Nile virus is the plasma membrane transporter of monocarboxylic acids MCT4. These genes and the pathways to which they belong thus become key to the understanding of virus-host cell interactions. It is also plausible that variation in some of the susceptibility and resistance genes could be associated with the likelihood of serious West Nile disease in individuals.

Krishnan et al. Nature. Published online August 6, 2008. 10.1038/nature07207

It Sure Beats a Colonoscopy

One way to monitor latent infections like HIV is to monitor the level of viral DNA in the body. If the invading cells happen to be the body's own cells gone awry, as in cancer, monitoring asymptomatic disease becomes trickier because of the necessity to distinguish tumor DNA from the rest of the DNA in the body. The existence of common mutations in certain cancers has made it possible to detect tumor DNA in plasma, and it is now possible to quantify the often minute quantities of mutant DNA in blood samples. Diehl et al. believe that this technology can be used to monitor disease in patients undergoing treatment for some cancers, and they illustrate this using plasma samples from individuals undergoing treatment for metastatic colorectal cancer. In comparison to carcinoembryonic antigen—the standard biomarker currently used to monitor these patients—circulating tumor DNA (ctDNA) was better able to predict recurrence of disease in their sample. Subjects who had ctDNA present in their blood after surgical resection of their tumors were much more likely to relapse within one year than were subjects in whom ctDNA could not be detected. As more data are collected on the oscillations of ctDNA during treatment and follow-up, this may become a useful and noninvasive biomarker to influence management strategies for cancer patients.

Diehl et al. Nature Medicine. Published online July 31, 2008. 10.1038/nm.1789

Mouse Mutants Yield Clues to Diamond-Blackfan Anemia

What do mouse ear color and red blood cell production have in common? In studies of two mouse mutants with pigmentary abnormalities, McGowan et al. found that defects in ribosomal proteins, which also cause Diamond-Blackfan anemia (DBA), are responsible for an epidermal melanocytosis that increases pigmentation of the footpads, tail, and ears. It is puzzling that defects in ribosome biogenesis would have such specific effects in the mouse mutants and in DBA, which is characterized by a defect

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
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in the production of red blood cells. McGowan et al. provide evidence that p53 stabilization may be a common feature of both outcomes but that cell-type specific pathways downstream of this p53 over-activation give rise to the phenotypes observed. In the case of the pigmentary abnormalities in mice, p53 activation increases expression of the Kit ligand, which, in turn, leads to epidermal melanocytosis. At least one of the mouse mutants also has a lower red blood cell count, which is reminiscent of DBA. In the bone marrow, these mice exhibit increased apoptosis of bone marrow progenitor cells, which presumably is triggered by p53 and could play a role in the pathogenesis of DBA.

McGowan et al. Nature Genetics 40, 963–970.

Copy-Number Variation and Schizophrenia

Many of the genetic association studies that have been published over the past few years have been dependent on the common disease-common variant hypothesis, which postulates that common genetic variation in the population contributes to the common disorders that have a genetic underpinning. However, if the disorder of interest reduces the likelihood that an individual will have children, perhaps the underlying genetic factors are not likely to be all that common. At least that's the theory that led Stefansson et al. to look for rare copy number variations (CNV) that contribute to schizophrenia. They used a population-based sample of trios and parent-offspring pairs to identify de novo CNVs and then tested them for association with schizophrenia in a large case-control sample. They report three deletions, on chromosomes 1q21.1, 15q11.2, and 15q13.3, that are significantly associated with schizophrenia. The International Schizophrenia Consortium was also interested in rare CNVs that contribute to schizophrenia. In a publication simultaneous with the work by Stefansson et al., they independently identified the same regions on chromosomes 1q21.1 and 15q13.3 as contributing to schizophrenia. Together, these reports suggest that rare structural variation may play a role in at least some cases of schizophrenia.

Stefansson. Nature. Published online July 30, 2008. 10.1038/nature07229

The International Schizophrenia Consortium. Nature. Published online July 30, 2008. 10.1038/nature07239