This Month in Genetics

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Predicting Alzheimer Disease via PET Scans

People with the APOE ε4 allele are at greater risk of being diagnosed with Alzheimer disease (AD) than are those without the allele. In fact, this is the major genetic risk factor for AD in the general population. If someone is homozygous for ε4, their risk is even higher, so it is possible to classify people into three AD risk groups on the basis of their APOE genotype. Even the homozygous APOE ε4 genotype doesn't destine someone for dementia, though, and there is nothing to be done about it anyway, so some people might just find this information nerve-wracking. Reiman et al. want to figure out how to better identify the people who are going to get AD before it actually happens. The point of this is not to put such people into a "doomed" category but, rather, to find an endophenotype for AD that can be monitored and that could serve as a way to test the effects of preventive therapies for AD. Reiman et al. use a PET radioligand that selectively binds to fibrillar aggregates of Aβ. These aggregates are a key neuropathological feature of AD, but we usually can't see them until autopsy. They compared PET scans on cognitively normal individuals from each of the three APOE ε4 genetic-risk groups, and they found that in several areas of the brain, fibrillar Aβ was associated with APOE ε4 carrier status. Because the level of genetic risk correlated with the level of fibrillar Aβ seen in the scans, this type of scan is promising as a way to more closely examine which individuals might be at risk of getting AD. This is supported by the finding that PET scans of people with a probable diagnosis of AD generally resulted in higher signals than were found in cognitively normal individuals and that APOE ε4 genotype no longer mattered when people had already progressed to having the disease. Larger and longitudinal studies are going to be a crucial step in determining how well this type of PET scan will actually predict whether somebody will get AD, but, if these results do hold true, these scans could identify those who need a preventive therapy, and it could aid in the development of that therapy.

Reiman et al. PNAS Early Edition. Published online April 3, 2009. 10.1073/pnas.0900345106.

Regulation of Neuronal Progenitor Proliferation by DISC1

As its name implies, *Disrupted in Schizophrenia 1* (*DISC1*) was originally identified in a single family in which a balanced translocation led to a high incidence of psychiatric disorders. The gene has since been implicated as a general risk factor for schizophrenia and other psychiatric disorders. The DISC1 protein regulates multiple steps in neurogenesis, but the mechanism by which it contributes to a range of psychiatric disorders has not been clear. Mao et al. provide multiple lines of evidence that DISC1 regulates the proliferation of neural progenitor cells in the developing brain and also in the adult dentate gyrus. Reductions in the level of DISC1 lead to reductions in neural progenitor proliferation, because these cells prematurely differentiate into neurons. This occurs through stabilization of β-catenin, and, in fact, the effects of DISC1 knockdown can be overcome through coexpression, in embryonic progenitor cells, of a mutant form of β-catenin that is resistant to degradation. The middleman between DISC1 and β-catenin is glycogen synthase kinase 3β (GSK3β). DISC1 interacts with and inhibits this enzyme, yielding increased stabilization of β-catenin and downstream activation of its target transcription factors. In mice, silencing DISC expression in the adult dentate gyrus leads to behaviors that are considered symptoms of schizophrenia and depression. These behaviors can be normalized if the mice are injected with a GSK3β inhibitor, further cementing the importance of this signaling pathway in the development of psychiatric disorders.

Mao et al. Cell 136, 1017–1031. 10.1016/j.cell.2008.12.044.

Enhancer Sequences Govern Cell-Type-Specific Gene Expression

Not all *cis*-regulatory elements are easily predicted by sequence gazing, so it has been tricky to identify some of these elements on a genome scale. Rather than looking for sequence motifs, Bing Ren's lab has been working on ways to identify these elements via characteristic patterns of protein binding and histone modification. Combining this knowledge, they now use this information to determine which elements play a major role in cell-type-specific gene expression. They performed chromatin-immunoprecipitation-based microarrays (ChIP-chip) on five human cell lines to compare patterns of CTCF (insulator-binding protein) and coactivator p300 binding, as well as to determine the chromatin signatures at promoters and enhancers. Whereas there is little variation across cell types in terms of the chromatin state at promoters and the CTCF

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DOI 10.1016/j.ajhg.2009.04.011.

binding, there are cell-type-specific histone modification patterns at enhancers that correlate well with cell-type-specific gene expression. These experiments suggest that enhancers are central to setting cell-type-specific gene expression patterns. The authors went on to use chromatin patterns to predict enhancers across the genome in HeLa cells and compared the results to those from K562 cells. Most of the enhancers are uniquely predicted in one cell type or the other, and when some K562-predicted enhancers were cloned into HeLa cells, the majority of them were inactive. On the basis of the cell-type specificity of enhancers and the number of enhancers predicted from just these two cell lines, the authors propose that a vast number of enhancers exists in the human genome.

Heintzman et al. Nature Advance Online Publication. Published March 18, 2009. 10.1038/nature07829.

Germline Variation Linked to Somatic Mutation

A somatic missense mutation in the JAK2 kinase is found in the majority of myeloproliferative neoplasms (MPN), which are characterized by clonal hematopoiesis. There are three diseases in this group, and they are defined by the cell lineage that predominates in the expanded population. These are: polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. Clearly, this single missense change, *JAK2*^{V617F}, is not the whole story behind the development of the MPNs, because the same mutation is associated with all three diseases and because this somatic change cannot explain the familial clustering of the MPNs. This led three groups to explore additional genetic variation contributing to MPNs. What each of these groups stumbled upon is the fact that a germline haplotype block that encompasses part of *JAK2* seems to predispose people to the acquisition of *JAK2*^{V617F} in *cis* to the haplotype. Does the haplotype lead to hypermutability in some way? Or, does the presence of the *JAK2*^{V617F} mutation on this particular haplotype background give it a selective advantage? These questions must be answered in order for us to unravel the intertwined germline and somatic contributions to the development of MPN.

Jones et al. Nature Genetics 41, 446–449. 10.1038/ng.334.

Olcaydu et al. Nature Genetics 41, 450–454. 10.1038/ng.341.

Kilpivaara et al. Nature Genetics 41, 455–459. 10.1038/ng.342.

The Role of Inflammation and Calcium in DMD

Calcium leakage in muscle cells is a key part of the pathologic process in Duchenne muscular dystrophy (DMD). Bellinger et al. explored this aspect of DMD and found that inflammation contributes to this part of DMD pathology. Perhaps not surprisingly, they report that inducible nitric oxide synthase (iNOS), which is made in inflamed tissues, is increased in an age-dependent fashion in muscle from the *mdx* mouse model of DMD. What is surprising is how this kicks off a downward spiral disrupting calcium homeostasis. The iNOS binds to the ryanodine receptors RyR1, which are calcium release channels in the sarcoplasmic reticulum. Ryr1 is nitrosylated by the nitric oxide produced by iNOS, which in turn depletes the stabilizing protein calstabin-1 from its complex with RyR1. Without calstabin-1, RyR1 channels are leaky to calcium, which moves from the sarcoplasmic reticulum into the cytosol where it activates calpains that produce muscle damage. Preventing this downward spiral by stabilizing the Ryr1 channels with a small molecule called S107 improves muscle function and reduces the histological evidence of muscle damage in *mdx* mice. The role of iNOS in DMD pathology is also supported by recent work by Villalta et al. (Human Molecular Genetics 18:482-496) who showed that *mdx* mice that are null mutants for iNOS exhibit less muscle fiber injury.

Bellinger et al. Nature Medicine 15, 325–330. 10.1038/nm.1916.