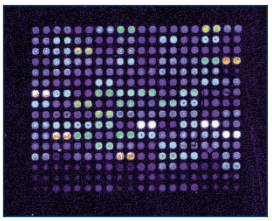
Highlights of This Issue

FMR1 and Parkinsonism

Loesch et al publish a fascinating article in this month's *GIM* (page 392) suggesting a link between modestly expanded *FMR1* alleles and Parkinsonism. The authors performed detailed clinical assessment and genetic analysis in 14 male carriers of premutation (PM) and grey zone (GZ) *FMR1* alleles and 24 non-carriers all taken from a sample of males with Parkinsonism. They found those carrying PM plus GZ alleles presented with more severe symptoms than controls matched for age, diagnosis, disease duration and treatment. The patients' motor scores and cognitive decline were significantly correlated with the size of their CGG repeat and with elevated levels of antisense *FMR1* and cytochrome C1 mRNA in leucocytes. While the study is small it intriguingly suggests that modest CGG expansion in *FMR1* alleles falling within the gray zone and lower end premutation zone may play a role in Parkinsonism.



Autism and 16p11.2

Autism spectrum disorders (ASD) not only represent a devastating clinical burden but also present a significant challenge to researchers. The ASDs have a well-documented and strong genetic underpinning yet even in this era of robust genomic analysis over 90% of cases remain etiologically unexplained. Highly penetrant micro-deletions and micro-duplications of 16p11.2 are known to contribute to ASD pathogenesis but the extent to which these variants contribute to the total burden of idiopathic ASD's had not been systematically investigated until Walsh et al. tackled the problem as reported in this month's issue (page 377). The investigators pursued a systematic literature review and meta-analysis to determine the prevalence of these variants among individuals with ASDs. In a combined analysis of 3613 idiopathic ASD cases from seven studies the prevalence of micro-deletions and micro duplications at this locus was 0.76%. Sporadic ASD cases showed only a slightly higher prevalence than did familial cases. The authors conclude that the number needed to test to identify one such variant in a patient with an ASD is 132. Such information should be of use to clinicians as they consider chromosomal microarray analysis in subjects with ASDs.

News Briefs

Risk SNPs, Dementia and an example of excellent science reporting

Two important papers were recently published in *Nature Genetics* [www.Nature.com Hollingworth et al and Naj et al; online 03 April 2011] that double the total number of genes implicated in the genesis of Alzheimer disease. Two groups studied a total of 54,000 subjects in the US and Europe by genome-wide association; the five loci which emerged as significantly linked to Alzheimer disease were particularly interesting because of their involvement with cholesterol transport and inflammation; processes which have been implicated biochemically for quite some time in this disorder.

While the identification of genes related to Alzheimer risk is important, its significance lies primarily in furthering our fundamental understanding of the disease and possibly in illuminating new drug targets. As expected, we witnessed the usual rash of popular headlines in response to these publications with words like "breakthrough" and even "cure" in their titles, reflective of the generally poor state of science journalism. However, I want to highlight a strikingly good article that came out in *Time's* online blog Healthland [healthland.time.com] by reporter Alice Park. I was particularly taken by its title: "New Alzheimer's genes: why they matter even if they don't change patient care". This article is a welcome example of responsible scientific journalism, appropriately and engagingly emphasizing the excitement surrounding this important set of papers but also taking a sober and realistic view of the work's real potential. After all, these newly recognized loci have, as one would expect, very low relative risk and will thus not be useful anytime soon in patient care. Their real value, as the *Times* article points out, is in furthering the important but naturally incremental progress of science. I encourage you to click on this story as an example of excellent science journalism; something we could use more of.

Highlights of the *AJHG*

This month in the *AJHG*, So et al publish an article entitled "Risk prediction of complex diseases from family history and known susceptibility loci, with applications to cancer screening". This article represents an attempt to develop a model by which clinically useful genomic risk data can be derived from GWAS-identified risk SNPs for possible use in screening populations. They created a statistical framework for risk prediction based upon genotype and family history, with allowance for genotypic information from family members.

The authors analyzed breast and prostate cancer with their model, finding that in breast cancer the 10 year risk varied from 1.1% in the 5th percentile to 4.7% in the 95th percentile. If one takes the average 10 year risk at 50 years old (2.39%) as the threshold for screening, the age for initiating screening ranged from 62 at the 20th percentile to 38 at the 95th percentile (some never reach the threshold). For women with one affected 1st-degree relative, the 10-year risks ranged from 2.6% (5th percentile) to 8.1% (95th percentile). The authors suggest that for some diseases genetic testing plus family history could stratify populations and be useful in screening. They may be correct, but such conclusions will need to be confirmed with actual (as opposed to modeling) data if one envisions limiting screening for a common disease such as breast cancer by such risk stratification. Finally, it remains unclear what added value genetic risk assessment has over other standard variables, at least at present.