This Month in Genetics

Kathryn B. Garber[1],*

Bedside Genetic Testing

Genetic variation influences individual response to the anticlotting drug clopidogrel, otherwise known as Plavix, leaving the approximately 30% of Western Europeans who are poor metabolizers of the drug at an increased risk of a cardiac event while on treatment. Doctors could switch to newer, more potent antiplatelet drugs that share the same drug target, but these are associated with increased risk of bleeding. It therefore seems unwise to use them on all patients. Theoretically, pharmacogenetic testing could be used for determining which drug should be prescribed on an individual basis, but, in an emergency situation, it does not seem feasible to wait on a genetic test result before moving forward with treatment. Point-of-care genetic testing could remove this barrier, and this is exactly what is tested in recent work reported by Roberts et al. in *The Lancet*. In a randomized trial involving patients undergoing stenting or angioplasty for acute coronary syndrome or stable angina, Roberts et al. examined whether bedside pharmacogenetic testing could be used for guiding medication choice and, subsequently, for reducing the proportion of poor clopidogrel metabolizers with high platelet reactivity after seven days of drug treatment. Nurses at the point of care could complete their genotyping strategy within an hour to identify carriers of the *CYP2C19*2* allele, which is a common allele associated with poor response to clopidogrel. These carriers could then be treated selectively with a more potent platelet inhibitor. Although this was a small study, Roberts et al. found that although none of the *CYP2C19*2* carriers in the genotyped group had a platelet reactivity above their threshold at seven days, 30% of those in the untested control group (who all received clopidogrel) were above this threshold and were therefore at an increased risk of a cardiac event. Although larger trials that assess clinical outcomes need to be performed, this at least provides a proof of principle for bedside pharmacogenetic testing.

Roberts et al. (2012). *The Lancet*. Published online March 29, 2012. 10.1016/S0140-6736(12)60161-5.

De Novo Mutations and Autism

Although large copy-number variants and mutations in known Mendelian disease genes all together explain a significant portion of autism cases, the underlying etiology remains unknown in the majority of cases. Some hypothesize that this is because rare variation in many different genes contributes to the disorder, a theory that is supported by three papers recently published by *Nature*. Traditional linkage and association methods are not able to detect this variation because it is rare and not expected to be passed through families. Thus, Neale et al., O'Roak et al., and Sanders et al. turned to exome-sequencing strategies in autism-affected families in an attempt to uncover rare, de novo SNVs that might contribute to autism. This is easier said than done; simply finding a de novo mutation in a person with autism is not enough for the disorder to be attributed to the mutation. In fact, modeling by Neale et al. suggests that most of this de novo variation is irrelevant to autism. To make sense of the variation, each group used further analyses to pull out the genes most likely to have relevance, including comparisons of the variation identified in the full sample of probands and interaction analyses to determine whether the genes with de novo variants interact closely with each other and with genes already known to contribute to autism. The genes that float to the top of the pile include those encoding sodium channels SCN1A and SCN2A, the chromatin remodeling factor CHD8, and an axon guidance cue, NTNG1. Are these sequence variants sufficient to cause autism? According to Neale et al., probably not. They propose that the de novo sequence variants must combine with other risk factors to yield autism. Discerning the global set of genetic risk factors in an individual will require much more research; O'Roak et al. estimate that several hundred loci might contribute to autism. One fact consistent between the three studies is the correlation between de novo sequence changes and paternal age, which is interesting given the association between paternal age and risk of autism.

Neale et al. (2012). *Nature*. Published online April 4, 2012. 10.1038/nature11011.

O'Roak et al. (2012). *Nature*. Published online April 4, 2012. 10.1038/nature10989.

Sanders et al. (2012). *Nature*. Published online April 4, 2012. 10.1038/nature10945.

A Window into the Future?

The value of personal genome scans is viewed as nil by some, but the fact that many people have sought these scans indicates that there is interest in genetic-based health predictions. Based on genetic associations, current scans use SNP genotyping. As we move to the predicted era of whole-genome sequencing for many people, will the predictions we glean from our genome get better? Roberts et al. used mathematical modeling based on twin registry

data to answer this question. They started with the idea that because monozygotic twins share a genotype, they share the same genetic risk for any disease. They could thus use registry data on the health status of the twins to estimate the distributions of genetic risk that would be consistent with the data. On the basis of these models and without genotyping the twins, they could then estimate the capacity for whole-genome sequencing to produce a clinically meaningful result for 24 diseases with diverse etiologies. They found that for 23 of these diseases, most individuals would receive negative results from whole-genome sequencing and that these will not reduce the risk of developing the disease by a substantial amount relative to the general population risk. On the other hand, more than 90% of tested individuals should receive a positive result that indicates a significantly increased risk of at least one disorder. Although admittedly based on modeling, this leaves me with a couple of questions: Is the identification of this risk enough to warrant whole-genome sequencing on a grand scale? And could we ever get to the point where we can find all of the relevant genetic variation for any specific complex disease anyway? I guess I need a window into the future in order to predict the answers myself.

Roberts et al. (2012). Sci. Transl. Med. Published online April 2, 2012. 10.1126/scitranslmed.3003380.

The Challenges of Prenatal Chromosomal Microarray

Compared to standard karyotyping, chromosomal microarrays (CMAs) have increased the diagnostic sensitivity of cytogenetic testing, and CMAs are now a first tier test for intellectual disability and autism. Trials are underway to move CMAs into the prenatal setting, which presents unique challenges. Rather than trying to explain a phenotype, as we do in a diagnostic setting, prenatal testing involves predicting the future, something that can be challenging when changes of uncertain significance or those associated with variable expressivity are detected. These challenges are discussed in two recent articles in a special issue of *Prenatal Diagnosis*. Wapner et al. use real CMA results generated via a National Institute of Child Health and Human Development (NICHD)-sponsored clinical trial of prenatal CMAs in order to illustrate several issues of uncertainty that can arise in prenatal CMA testing. McGillivray et al. explore ethical aspects of the use of prenatal CMAs; such aspects are patient autonomy in decision-making, informed choice in genetic testing, and the moral responsibility of the physician when an elective termination is performed on the basis of CMA results. Both articles stress the role of appropriate counseling before and after the test to help families make the best use of prenatal CMA. It is important to keep in mind that uncertainties that arise from prenatal CMAs are not new; there are no guarantees in prenatal testing no matter what approach is taken. On the other hand, the closer you look at the genome, the more you'll find. This type of discussion is therefore important for ensuring the most effective delivery of this testing to patients.

McGillivray et al. (2012). Prenatal Diagnosis 32, 389–395. 10.1002/pd.3849.

Wapner et al. (2012). Prenatal Diagnosis 32, 396–400. 10.1002/pd.3863.

On Second Look…

For years, the estimated number of imprinted genes in the genome was somewhere around 100–200. The advent of whole-transcriptome sequencing (RNA-Seq) provided an opportunity for researchers to look genome-wide for imprinted genes, an approach that was taken by a couple of recent papers that examined transcripts from reciprocal mouse crosses (*Science* 329, 682–685 and *Science* 329, 643–648). The data therein suggested that the number of imprinted genes might, in fact, be an order of magnitude higher than previously estimated, which startled many researchers. DeVeale et al. were fascinated by this finding but had problems confirming it. They did further analyses of the RNA-Seq data and found that, in fact, many of the novel imprinted genes discovered via RNA-Seq are actually false positives. To estimate the false-discovery rate, the researchers did a mock reciprocal cross in which they used RNA-Seq data from samples with the same parental backgrounds (rather than reciprocal backgrounds) and found almost as many "imprinted" gene calls as were observed with the true reciprocal crosses. They also found that SNPs from the same coding exon but from different sequence reads often gave discrepant results for allele-specific expression, which is hard to reconcile. DeVeale et al. revised the estimate of imprinted genes back down closer to what it had been, and they also use their analyses to propose criteria that could be used to predict the likelihood that a putative imprinted gene will be validated.

DeVeale et al. (2012). PLoS Genetics 8, e1002600. 10.1371/ journal.pgen.1002600.

This Month in Our Sister Journals

A New Use for the TDT

Picking which allele a child inherits from a parent is like a flip of a coin, or so we like to say when we're teaching basic genetic principles. Sometimes, this is not true and there is a deviation from this randomness that is termed transmission distortion. This could have something to do

with an allele influencing the gametes, such as a process that alters the allele ratios during meiosis or one that influences how likely it is that a gamete will lead to a successful fertilization. This distortion could, on the other hand, reflect a difference in the viability of the resulting embryo. Examples of transmission-distorting alleles have been found in models systems, but little is known about them in humans. Meyer et al. were interested in studying this phenomenon in humans on a genome-wide scale. The tactic they took used the transmission disequilibrium test, or TDT. The TDT was designed to look for alleles that were not passed randomly from parents to children as a way to detect genetic association with traits of interest, but Meyer et al. realized it could instead be used to detect transmission distortion from heterozygous parents regardless of the phenotype of the children. They applied the TDT to three large datasets: the Framingham Heart Study (FHS), the AGRE sample, and a Hutterite sample. One promising candidate region on chromosome 10 exhibits transmission distortion in the AGRE sample and overlaps a region that had previously shown distortion in a HapMap sample. Beyond this, their analyses turned out to be very sensitive to genotyping error, which confounded the results from the FHS and Hutterite samples. Turning lemons into lemonade, the authors propose that this type of analysis could be used to identify SNPs that are more subject to genotype error via array-based genotyping platforms.

Meyer et al. (2012). Genetics. Published online February 29, 2012. 10.1534/genetics.112.139576.