This Month in Genetics

Kathryn B. Garber[1,*]

Short-Term Impact of Direct-to-Consumer Testing

Like it or not, direct-to-consumer genetic analysis is widely available to the general public, albeit at a significant out-of-pocket cost. Whereas proponents argue that anybody should be able to get their own genetic information and that these tests could have a positive impact of health-related behaviors, opponents say they lack clinical validity and utility and may lead to increased anxiety and subsequent use of unnecessary screening procedures. Bloss et al. surveyed more than 2000 individuals at baseline and three months after receiving genetic risk information for 22 conditions, based on the Navigenics Health Compass, and found no evidence that direct-to-consumer testing affects health-related behavior in the short-term. The vast majority of subjects in the study (>90%) exhibited no distress related to the genetic testing, but the tests also didn't have a positive impact on health behaviors, in that there was no change to dietary fat intake or exercise behavior as a result of the genetic screen. There also was no increase in the number of screening tests completed by the time of first follow-up, although approximately half of the subjects indicated their intent to do so. One outcome that does need to be addressed is the fact that 10% of participants elected to consult a genetic counselor in relation to their genetic profile, and greater than 25% discussed the results with their physician. Certainly, the healthcare system overall will need to be able to handle this increased interest in genetics as more people opt for genome-wide profiling.

Bloss et al. (2011). NEJM. Published online January 12, 2011. 10.1056/NEJMoa1011893.

Epimutations Could Make a Significant Contribution to Cowden Syndrome

Mutations in *PTEN* cause the cancer-predisposing Cowden syndrome, but a significant number of people who meet the diagnostic criteria do not have a mutation in *PTEN* or in *SDHB* or *SDHD*, which lead to a similar phenotype. Even fewer people with Cowden-like syndrome, who have features of Cowden syndrome but do not meet the diagnostic criteria, have documented mutations in these genes. Because epigenetic alterations are known to play a role in cancer development and progression, Bennett et al. collected a group of patients with Cowden syndrome and Cowden-like syndrome in whom mutations could not be found. Hypermethylation upstream of *PTEN* was documented in peripheral lymphocytes from 45 of 123 individuals, but, unexpectedly, this was not associated with decreased *PTEN* expression. Instead, the methylation influenced expression of *KILLIN*, a gene that shares a transcriptional start site with *PTEN* but is transcribed in the opposite direction. In addition to implicating a new gene in Cowden syndrome, if these results hold up, it would alter the scheme for genetic testing in patients, particularly those with Cowden-like syndrome, because *KILLIN* methylation accounts for a larger fraction of these patients than do *PTEN* mutations.

Bennett et al. (2010). JAMA 304: 2724–2732. 10.1001/jama.2010.1877.

Sequencing the Future

When there are limits to the amounts of DNA that can be genotyped for a reasonable cost, we target genetic screens to the people most likely to carry a mutation. That's the rationale behind the targeting of certain carrier screens, including cystic fibrosis to those of European descent and Tay-Sachs disease to those of Ashkenazi Jewish descent. Indeed, we not only focus these screens on particular populations, we also limit the screens to particular disease mutations in that population. These limitations mean that some carriers are missed and many severe recessive disorders go unscreened. What happens when we aren't as hampered by technological limitations? Bell et al. show that you can create screens that identify carriers for more than 400 severe recessive childhood disorders. Moreover, their screen uses target enrichment and next generation sequencing techniques, so the screens detect most relevant mutations, rather than a hand-picked subset. Although this screening approach highlights the potential future of carrier screening, it also sheds light on potential kinks for its use in populations. Of the sequence variants flagged as disease mutations by their filtering criteria, 74% of them turned out to be polymorphisms. Even the fact that a mutation was cited in the literature did not guarantee it was one; in fact 27% of cited disease mutations were found to be likely polymorphisms or to be misannotated. Thus, as with other genomics applications, the trick now lies in interpretation rather than in production of sequence.

Bell et al. (2011). Science Translational Medicine, 3: 65ra4. 10.1126/scitranslmed.3001756.

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
DOI 10.1016/j.ajhg.2011.01.013.

Did *HTR2B* Make Them Do It?

Recent work by Bevilacqua et al. argues that a nonsense codon in *HTR2B*, which normally encodes a subtype of serotonin receptor, is found at higher rates in a set of violent criminals from Finland, and they attribute this to increased impulsivity in carriers of the allele. The "impulsivity" allele is so far only found in Finland, and the authors extrapolate that there are 100,000 carriers in Finland. Finland is not exactly known as a hot-bed of criminal and rash behavior, so the lack of impulse control because of this mutation, if there is any, is not strongly penetrant. One environmental contributor that could influence its phenotypic expression is alcohol; in their original association study, almost all of the crimes committed by the carriers of the nonsense *HTR2B* allele occurred when the individuals were under the influence of alcohol. Particularly given historical missteps in declaring "criminality genotypes," caution must be urged in the interpretation of this work.

Bevilacqua et al. (2010). Nature 468: 1061–1066. 10.1038/nature09629.

Two MicroRNAs Responsible for Delayed Hemoglobin Switching in Trisomy 13

Because of the many genes involved and the complexity of the resulting phenotypes, it can be difficult to attribute any one component of an aneuploidy syndrome to a culprit gene or genes. Careful comparisons of phenotype and the chromosomal composition of individuals with partial aneuploidy for a particular chromosome can sometimes limit the relevant chromosome region, but—even so—the resulting list of candidate genes can be too long to wade through. One feature of the trisomy 13 phenotype is the delayed switch to and persistence of fetal hemoglobin (HbF). Through use of a bioinformatics approach, Sankaran et al. implicate two microRNAs on chromosome 13 as being key to this process, and further investigation of their target gene leads them to expand the description of the hematopoietic phenotype caused by trisomy 13. Analysis of potential targets for these miRNAs, miR-15a and miR-16-1, leads them to MYB, which is a negative regulator of HbF expression and is also crucial for normal differentiation kinetics of adult erythroid cells. This led Sankararn et al. to examine histological samples from individuals with trisomy 13 and to discover a previously unrecognized aspect of the phenotype: a dramatic elevation in the number of megakaryocytes, which also had an abnormal nuclear morphology. Beyond informing our understanding of the trisomy 13 phenotype, we now better understand the regulation of erythroid differentiation and globin gene expression.

Sankaran et al. (2011). PNAS. Published online January, 4, 2011. 10.1073/pnas.1018384108.

This Month in our Sister Journals

Perinatal Lethal Osteogenesis Imperfecta: Will It Happen Again?

Both autosomal dominant and autosomal recessive forms of perinatal lethal osteogenesis imperfecta (OI) have been documented, and this complicates genetic counseling for families who have had an affected infant. The recurrence risks in these families can range from extremely low, in the case of a new dominant mutation, up to 50% if one of the parents is mosaic for a dominant mutation. Pyott et al. use data collected over the course of several years to better calculate recurrence risks for different categories. In 16% of cases that were due to a dominant mutation in one of the type I collagen genes, parental somatic mosaicism was documented, leaving these families at much higher recurrence risk than the general recurrence estimate of 1.3% after the birth of a first affected child. An additional sample of families with more than one affected pregnancy allows them to demonstrate that parental mosaicism of a dominant mutation is a more common cause of familial recurrence than are autosomal recessive mutations. In this sample, the recurrence risk in families with parental mosaicism turns out to be 27%, which is very close to the 31% recurrence risk observed in families with OI because of recessive mutations. Mutation identification in affected children and analysis of parental samples can help to assign families to different categories for more accurate risk assessment.

Pyott et al. (2011) Genetics in Medicine. Published online January 13, 2011. 10.1097/GIM.0b013e318202e0f6.