IN THIS ISSUE

Detection of fetal trisomy 13, 18, and 21 via maternal plasma analysis

see page 296

©iStockphoto.com

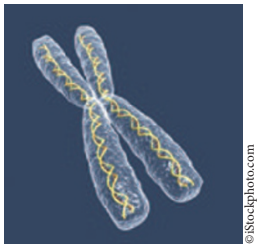
Next-generation sequencing (NGS) is realizing its promise rapidly in the context of clinical medicine, and one of the first routine applications of such technology will probably be for screening in the prenatal setting. Recently, *GIM* brought you a study demonstrating the feasibility of diagnosing Down syndrome through analysis of fetal DNA circulating in maternal plasma early in pregnancy. In this issue, the same group expands this technique to the other common trisomies, 13 and 18.

Sixty-two trisomy 18 and 12 trisomy 13 pregnancies were selected from a cohort of 4,664 pregnancies and, along with matched euploid controls, were tested using a laboratory-developed NGS approach. Among the 99.1% of samples interpreted (1,971/1,988), the observed trisomy 18 and trisomy 13 detection rates were 100% (59/59) and 91.7% (11/12) at false-positive rates of 0.28% and 0.97%, respectively. If *z*-score cutoffs for trisomy 18 and trisomy 13 were raised slightly, the overall false-positive rates for the three aneuploidies could be as low as 0.1% (2/1,688) at an overall detection rate of 98.9% (280/283) for common aneuploidies. An independent academic laboratory confirmed performance in a subset.

Thus, in high-risk pregnancies, sequencing circulating cell-free DNA detects nearly all cases of Down syndrome, trisomy 18, and trisomy 13, at a low false-positive rate, potentially reducing invasive diagnostic procedures and related fetal losses by 95%.

Impressive laboratory performance in the diagnosis of fragile X syndrome

see page 306



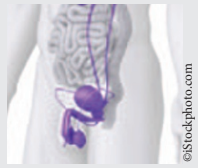
©iStockphoto.com

A great deal rides on the accuracy and reliability of genetic testing. The stakes are high and the task difficult, especially when considering complex tests such as those used to detect trinucleotide repeat expansion for the diagnosis of fragile X syndrome. Weck et al. report on almost a decade of laboratory performance with respect to diagnosis of this condition. Individual laboratory responses were analyzed for accuracy of genotype determination (normal, gray zone, premutation, or full mutation) and size analysis of the *FMR1* trinucleotide repeat region. Overall, the results are encouraging, with laboratories demonstrating analytical sensitivity of 99% and 96% for detection of full mutations associated with fragile X syndrome in males and females, respectively. For premutation detection, analytical sensitivity was 98% and analytical specificity was 99.9%.

The study concludes that molecular genetic testing for fragile X syndrome has demonstrated excellent sensitivity and specificity among laboratories participating in annual proficiency surveys. Also, encouragingly, the accuracy of allele sizing significantly improved over the study period.

NEWS BRIEFS

A bit of progress in understanding prostate cancer genetics



©iStockphoto.com

The genetics of prostate cancer has proven surprisingly difficult to unravel. Family history has long been known as a prostate cancer risk, and, through GWAS more than 30 SNPs have been identified that are linked to prostate cancer risk. However, the magnitude of risk elevation attributed to each individual SNP is low, and these SNPs in aggregate account for only an estimated one-quarter of familial risk. Thus, our genetic understanding of prostate cancer has not translated into clinically useful information. This situation stands in stark contrast to that for breast and ovarian cancer, where a minority of cases result from the inheritance of highly penetrant mutations in *BRCA1/2* and testing for such mutations has become the standard of care for a significant minority of breast cancer patients.

However, some progress has been made, as recently reported by Ewing et al. in the *New England Journal of Medicine* (2012;366:141–149). In a large multicenter study, the authors examined a region on chromosome 17q21–22 that had previously been identified as a possible location of a prostate cancer–susceptibility gene. The authors screened more than 200 genes in this region by sequencing germline DNA from 94 unrelated patients with prostate cancer from families with linkage to the candidate region. Probands from four families were discovered to have a rare but recurrent mutation (G84E) in *HOXB13*, a homeobox transcription factor gene known to play a role in prostate development.

The carrier rate of the G84E mutation was increased by a factor of approximately 20 in 5,083 unrelated subjects of European descent who had prostate cancer, with the mutation found in 72 subjects (1.4%), as compared with 1 in 1,401 control subjects (0.1%), a highly statistically significant result. The mutation was significantly more common in men with early-onset, familial prostate cancer (3.1%) than in those with late-onset, nonfamilial prostate cancer (0.6%) and appears to increase risk by 10- to 20-fold.

The recurrent nature of the G84E change and a reported lack of any truncating mutations in *HOXB13* in patients with prostate cancer suggest a carcinogenic mechanism that is more consistent with a gain of function (oncogene) than with a loss of function (tumor-suppressor gene).

Thus, although this mutation appears to be relatively rare, a long-sought highly penetrant prostate cancer mutation appears to have finally been identified. Although the variant accounts for a small fraction of all prostate cancers, this finding may have clinical utility in the analysis and counseling of families with early-onset prostate cancer and may provide new mechanistic insights into this common cancer.

RESEARCH HIGHLIGHTS

NEWS BRIEFS

Richard King Trainee Award winner for 2011

In our field's well-justified excitement over advances in genomic sequencing, it's easy to forget that other fundamental aspects of genomic structure remain critical to understand. One such basic—and often overlooked—issue is determining the *cis-trans* relationships of alleles.

It is in this context that we are delighted to announce that the winner of our annual trainee award is Neng Chen, PhD, Stanford University School of Medicine, Stanford, California, who coauthored "Allelic Discrimination of *cis-trans* Relationships by Digital Polymerase Chain Reaction: GJB2 (p.V27I/p.E114G) and CFTR (p.R117H/5T)," published in the December 2011 issue of *GIM*. In this article, the authors detail a novel method for determining the *cis-trans* status of alleles in two important clinical contexts: cystic fibrosis and deafness. Importantly, the approach that they describe holds promise for more general application as it does not fully depend on the specific nucleotide changes, enabling efficient assay design and practical implementation of allelic discrimination.

Through a gift from the ACMG Foundation, Dr Chen was awarded $1,000 as well as travel, hotel, and registration costs to attend the Annual ACMG Meeting in 2012.

A Call to Trainees!

Submit your research to *GIM*!

The Annual Richard King Trainee Award for Best Publication

In order to encourage genetics trainees in their professional development, *Genetics in Medicine* and The American College of Medical Genetics Foundation have an annual award recognizing an outstanding research publication by an ABMG trainee. The award consists of $1,000 cash prize to the recipient as well as travel, hotel and registration costs for the annual ACMG meeting that year. Eligible individuals are ABMG trainees who have been first author or corresponding author on a paper published the preceding calendar year in *Genetics in Medicine*.

Eligible trainees include those in the following programs:
Medical Genetics (MDs)
Combined Internal Medicine/Genetics
Combined Pediatrics/Genetics
Combined OBGYN/Genetics
Clinical Biochemical Genetics
Clinical Cytogenetics
Clinical Molecular Genetics
Subspecialty-Medical Biochemical Genetics
Subspecialty-Molecular Genetic Pathology

Eligible trainees should identify themselves upon submission of manuscripts to *Genetics in Medicine*. Original research, brief reports and educational reports are eligible categories, but other categories, such as review articles, are not. The editorial board of *Genetics in Medicine* will determine the winning trainee and presentation of the award will be made each year at the American College of Medical Genetics Annual Meeting.