# IN THIS ISSUE

## Massively parallel sequencing in Leber amaurosis

see page 576


Massively parallel sequencing (MPS) continues to prove its worth in both the research and, increasingly, the clinical arena. This month we're happy to bring you a report from Ghent and Brussels, Belgium, in which MPS was employed for early molecular diagnosis in patients with Leber congenital amaurosis (LCA). Like many of the hereditary eye diseases, LCA is highly genetically heterogeneous with at least 16 mutated genes thus far described. Defining the mutation responsible for LCA in any given patient is challenging and has taken on new urgency because of recent progress in gene therapy that requires knowledge of the responsible mutation.

Coppieters *et al.* designed an assay for multiplex sequencing of all 236 exons from 16 known LCA genes. They deployed their assay in 17 LCA patients without previously identified mutations; the causal genetic defect and a single heterozygous mutation were identified in 3 and 5 of the patients, respectively. Such assays will probably soon become the standard of care for diagnosis of genetically heterogeneous disorders. I suspect that eye diseases will be in the forefront of such applications given their heterogeneity and the recent exciting progress in gene therapy, which provides added impetus. *—James P. Evans, Editor-in-Chief*

## Array analysis complements DNA sequencing for mutation detection

see page 594


The advent of massively parallel sequencing promises to transform the ability to detect disease-causing mutations in clinical practice. However, in our enthusiasm to embrace this powerful new technology, we must not forget that some classes of mutations are transparent to many sequencing strategies. For example, most exon-sized deletions will go undetected by whole-exome sequencing, and even in the context of whole-genome sequencing, deletions can go undetected without proper informatics processing. Until now there has not been a systematic assessment of the frequency of exonic deletions and duplications for most Mendelian disorders. To address this need, Aradhya *et al.* designed a comparative genomic hybridization (CGH) test to probe exons in 219 genes associated with known genetic disorders. The investigators tested 3,018 individuals who had been referred for genetic testing. The exon array identified 98 partial or whole-gene deletions and two duplications, for an overall detection rate of 3.3%. Of 138 individuals tested for recessive disorders, 10.1% had an intragenic deletion, and of 313 tested for X-linked disorders, 3.5% carried a deletion or duplication. Limitations of the study included a 169-bp minimum size for deletion detection and an array design that did not include promoters. Nonetheless, these data suggest that CGH testing should routinely supplement sequence analysis for Mendelian disorders. *—Karyn Hede, News Editor*

# NEWS BRIEFS

## Gene patents are dead...sort of


There has been much action recently in the realm of gene patents. In March, the Supreme Court issued a unanimous (!) decision in the case of Prometheus v. Mayo that has important implications for gene patents. Prometheus Laboratories had claimed a patent on a "method" that consisted essentially of administering a drug to an individual, measuring that drug's metabolites, and adjusting the dose of the drug accordingly (seriously; I didn't make this up). In a refreshingly logical turn of events, the Supreme Court ruled that such a patent claim was invalid, stating that to allow such a claim would "inhibit further discovery by improperly tying up the future use of laws of nature." Thus, it would seem that broad methods claims, such as patenting the association between high risk for a disease and mutations in a given gene, are dead. Good riddance.

However, that's not the whole story. Although many of us saw such methods claims as the most mischievous types of patent claims, we still have no clarity on whether genes themselves can be patented. In the case that many hoped would settle this question, brought against Myriad Genetics over the *BRCA1/2* gene patents, the Supreme Court has returned the case to the lower court, directing them to reconsider it in light of the Prometheus decision. So we won't have legal clarity on this fundamental issue for some time to come.

It is my own opinion that several recent developments profoundly undermine the ultimate legitimacy of gene patents, including the Prometheus decision and new technologies such as massively parallel sequencing that do not rely on "isolation and purification" steps for sequencing. However, I'm also afraid that such patents will continue to cause harm while in their protracted death throes. *—James P. Evans, Editor-in-Chief*

## First brain-only mutation identified


Investigators seeking the cause of a rare neurologic disorder in which half the brain becomes abnormally enlarged provide the first confirmed report of a brain-only somatic mutation. The study was possible because the severe seizures that accompany hemimegaencephaly (HMG) necessitate excision of brain tissue, providing samples for further analysis. Ann Poduri and coinvestigator Christopher Walsh of Children's

## NEWS BRIEFS

Hospital and Harvard Medical School, Boston, studied resected brain tissue from eight HMG patients and reported their results in the April 12 issue of *Neuron*. In one case, the patient had acquired a known activating mutation in the *AKT3* gene, which encodes a protein kinase known to be highly expressed in the brain. The point mutation (c.49G/A, creating p.E17K), which is not present in this patient's blood cells, is paralogous to known mutations causing overgrowth syndromes in the *AKT1* and *AKT2* genes. Two additional cases showed brain-only trisomy of chromosome 1q, including the *AKT3* gene. As techniques are developed for testing DNA from smaller tissue samples, the possibility emerges of identifying somatic mutations for tissue-limited disorders with less obvious physical manifestations. —*Karyn Hede, News Editor*