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Tests of unknown significance

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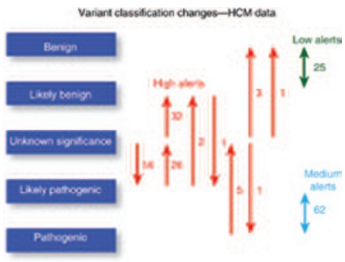

Clinical genetic testing and the increased use of whole-genome sequencing are rapidly widening the gap between the volume of information generated and the medical community's ability to keep up to date. Take the case of genetic variants of unknown significance, which are identified by the thousands in broad sequencing applications. Immediate issues arise as to where the responsibility lies for informing physicians and patients of clinically actionable information. In this issue, investigators at Partners HealthCare Center for Personalized Genetic Medicine, in Cambridge, MA, argue that information technology support to provide timely updates must be developed in parallel to the tests themselves. The center's Laboratory for Molecular Medicine currently tracks 10,155 unique variants in 219 clinically relevant genes. Tracking changes in variant classification for just one genetic disease—hypertrophic cardiomyopathy—revealed that over a six-year period, new knowledge pertaining to genetic variants altered 756 patient reports in a clinically meaningful way. To address this growing knowledge gap, Partners launched a health care–provider Web interface to provide updates as new information on genetic variants becomes available, with the intention of eventually integrating it into a unified electronic health record. Through their experience, the authors make the point that IT support for genomic testing must develop in parallel with the tests themselves. *—Karyn Hede, News Editor*

Microarray analysis misses some cases of UPD

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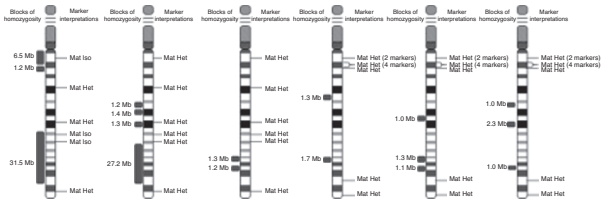
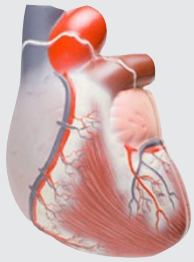


The reliability of chromosomal microarray analysis (CMA), a now-standard test for detection of copy-number variants in suspected cases of autism spectrum disorders, is relatively untested for detecting cases of uniparental disomy (UPD), the inheritance of both homologs of a chromosome pair from a single parent. To help assess the test's diagnostic appropriateness in instances of suspected UPD, investigators at the University of British Columbia, Vancouver, retrospectively analyzed 11 confirmed cases of UPD in chromosomes 7 and 15, which contain clusters of imprinted genes associated with recognizable syndromes, most prominently Prader–Willi syndrome. CMA failed to detect UPD in 4 of the 11 cases. In all 4 cases, complete heteroUPD suggested a final failure of maternal recombination. It is unclear how many cases of UPD on other chromosomes may also be missed by CMA. More sensitive single nucleotide polymorphism–based CMA should detect most UPD cases, but it will not pick up cases of complete heteroUPD. If a strong clinical suspicion remains after CMA analysis, additional testing is warranted. *—Karyn Hede, News Editor*

NEWS BRIEFS

A genetic policy statement from the American Heart Association



As we struggle with how to handle the increasing permeation of medicine by new genetic technologies and knowledge, we geneticists have often felt lonely. It is therefore nice to see a thoughtful, detailed, and broad-ranging analysis along with a set of policy recommendations from the American Heart Association (AHA).

The AHA panel, chaired by Euan Ashley of Stanford University, advocates for expansion of antidiscrimination legislation, for genetic testing and counseling to take place at specialized centers, and for an evidence-based assessment of pharmacogenomic applications before clinical actions are based on genotype. The statement provides an intelligent discussion of the role of genome-wide association study–identified risk single-nucleotide polymorphisms in clinical medicine and encourage further research before such risk factors for common disease are acted on clinically. The panel also called for a large investment in infrastructure to catalog human genetic variation as well as for genetic research in general.

Ashley states, "Genetic testing provides a tremendous opportunity but also a challenge in being responsible with that information. If the information is available, how best do we use it to really improve care for individual patients?"

The panel has done an admirable job of reflecting excitement about the potential of genetics without devolving into hype or wishful thinking; throughout the document they strongly advocate for an evidence-based approach to the incorporation of genetics into cardiology. I highly recommend its report, which can be found at: http://circ.ahajournals.org/content/early/2012/05/24/CIR.0b013e31825b07f8.citation.

—James P. Evans, Editor-in-Chief

Complex-disease risk predictions may not change with genetic data

A new statistical analysis may let the wind out of the sails of medical geneticists and physicians expecting genetic data to help guide clinical decision making for common yet complex diseases. Much of the payoff from mass genomic screening is expected by

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many to lie in the development of statistical algorithms that take into account the synergistic effects of genetic and environmental factors. But when a research team from the Harvard School of Public Health ran a series of simulations designed to test the power of synergistic interactions among common diseases, they found that those interactions modified disease risk by a paltry 1–3%. The research team studied three diseases for which there are known genetic and environmental factors: breast cancer, rheumatoid arthritis, and type 2 diabetes. They compared statistical models that included simulated gene–environment interactions with models that included only marginal effects—effects that contribute only small, individual, and incremental data to classifying disease risk factors. The authors conclude that teasing out those interactions, even if possible, will probably not change the advice that doctors give patients for most common diseases. However, they note that the study is relevant for only common, multifactorial disease and should not discourage research to understand the interplay between genes and the environment, which can lead to a better understanding of disease origins and improve prevention strategies. The study appeared in the *American Journal of Human Genetics* online on 24 May 2012 and in the 8 June 2012 print issue. *—Karyn Hede, News Editor*