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Genome-wide CNV testing will uncover clinically actionable incidental findings

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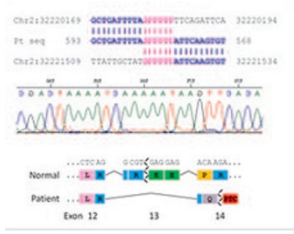

As genome-wide studies enter the clinic, evidence continues to mount that potentially clinically actionable incidental findings can be expected with some regularity. In this issue, Boone et al. describe an array of incidentally discovered copy-number-variant (CNV) mutations that may increase the risk of adult-onset disease and may be clinically actionable. The group performed array comparative genomic hybridization (aCGH), which can detect deletions, duplications, and rearrangements as small as one exon, on just over 9,000 individuals who had been referred because of suspicion of a genetic disorder. In addition to detecting CNVs relevant to the referring condition, the research team identified 83 CNVs affecting late-onset-disease genes. Frustratingly, half of the variants discovered were of unknown clinical importance. The authors suggest that, given the nearly 1 in 100 chance that potentially clinically relevant incidental genetic alterations will be revealed, patients should be made aware of this possibility before being asked to consent to testing. *—Karyn Hede, News Editor*

Parsing the incidentalome

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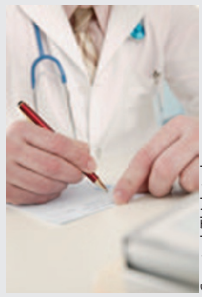
Given the large number and heterogeneous nature of genomic variants generated any time genome-scale analysis is performed, informatic approaches will need to be developed that assist in clinical decision making regarding their interpretation and to guide the return of such results. One such attempt is described by Berg et al. in this issue. Using an automated filtering system that categorizes genomic variations by potential clinical significance, the authors conducted a test run of 80 whole-genome sequences gleaned from publicly available sources. After they had applied a series of filters designed to reduce the probability of identifying variations unlikely to cause disease, the algorithm effectively reduced the number of variants requiring human review and identified incidental variants with likely clinical relevance, including about nine variants per person indicating carrier status for recessive disorders. The proposed filtering approach excludes typically benign missense mutations as well as variants within intergenic regions and introns. Although it decreases overall sensitivity, the authors argue that a stringent cutoff ensures high specificity, reduces the need for manual review of results to a manageable level, and is both necessary and advisable when dealing with incidental findings that represent, by definition, a low *a priori* risk of disease. The proof-of-concept approach is flexible and amenable to changes as more information about disease risk associated with various variants becomes available. The results also demonstrate the inadequacy of current mutation databases, an important issue because the ultimate utility of any analytical scheme in a genomic context will require a well-curated and regularly maintained universal, publicly available database of known gene variants. *—Karyn Hede, News Editor*

NEWS BRIEFS

Doctors often mistakenly order inappropriate genetic tests



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As the ordering of genetic tests enters mainstream medical practice, educating physicians on when and how to order these tests will become paramount. The few studies that have examined physician understanding of genetic testing generally indicate a knowledge gap. Recently, the *Cancer Journal* dedicated an entire issue (July–August 2012) to the status of genetic testing for cancer. Brierley et al. presented a review of medical errors resulting from incorrectly ordered genetic tests associated with various types of cancer. They cited a survey of New York obstetrician–gynecologists who reported that office staff often completed genetic test requisitions, reviewed test results, and gave test results to patients over the phone. The review concluded that it is unrealistic to expect the average clinician to provide genetic counseling and testing services. The use of genetic counselors to review physician test orders is one solution suggested by ARUP Laboratories, a national reference laboratory associated with the University of Utah. It recently self-published a review of all the molecular genetic tests conducted in 2010 at its Utah facility. A review of records by its staff genetic counselors showed that doctors incorrectly ordered complex genetic tests about 30% of the time. The study also found the doctors' most frequent errors were requesting the wrong test and confusing rare diseases that have similar names. The study concluded that having genetic counselors review and correct orders saved about $36,000 per month in health-care costs. *—Karyn Hede, News Editor*

The 1000 Genomes Project reveals we all have genetic baggage, but that's OK

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The second phase of the 1000 Genomes Project, designed to provide a baseline for the normal range of human genetic variation, reports that all the 1,092 healthy individuals from 14 different populations sampled have variants that might be considered deleterious. The project's consortium reported in *Nature* on 1 November that nearly all the common variants it found had previously been described, but 58% of the low-frequency variants and 87% of the rare variants were new.

NEWS BRIEFS

The study participants harbored from 130 to 400 of these genetic stowaways. Of these variants, 10 to 20 have been implicated as causing damage or destruction to protein function and 1 or 2 are associated with cancer. Yet the individuals were healthy when they became study participants, suggesting that our assessment of pathogenicity is often in error or that we all carry genetic baggage that only under certain circumstances can be considered a risk to health. The findings suggest that rare variants should be interpreted with caution and within the context of geographic or ancestral genetic background. The challenge now will be to discriminate the variants that truly pose genetic risks to patients' health from harmless inherited stowaways that won't ever bother them. The study's haplotype map of 38 million single-nucleotide polymorphisms, 1.4 million short insertions and deletions, and 14,000 large deletions should assist in attainment of that goal.
—Karyn Hede, News Editor

Genetics in Medicine | Mission Statement

Genetics in Medicine is a monthly journal committed to the timely publication of:

- Original reports which enhance the knowledge and practice of medical genetics
- Strategies and innovative approaches to the education of medical providers at all levels in the realm of genetics

As the official journal of the American College of Medical Genetics and Genomics (ACMG), the journal will:

- Provide a forum for discussion, debate and innovation concerning the changing and expanding role of medical genetics within the broader context of medicine
- Fulfill our responsibility to the College membership through the publication of guidelines, policy statements and other information that enhances the practice and understanding of medical genetics

Finally, as genetics becomes increasingly important in the wider medical arena, we will be an accessible and authoritative resource for the dissemination of medical genetic knowledge to providers outside of the genetics community through appropriate reviews, discussions, recommendations and guidelines.