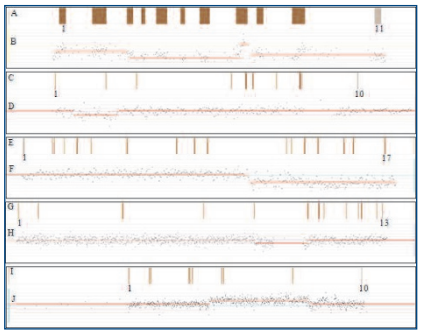
Highlights of This Issue

Sequencing is not enough

The detection of deleterious mutations in the clinical laboratory is challenging in part because of the heterogeneous nature of disease-causing mutations which can arise. Sequencing has traditionally been the mainstay of mutation detection and is increasingly practical on a large scale. However, while it reliably detects missense mutations, nonsense mutations and small indels, a non-trivial fraction of deleterious mutations are transparent to sequencing strategies. Such "invisible" mutations include large rearrangements and exon sized deletions within genes. A variety of techniques have been employed to search for such deletions and rearrangements including Southern blotting, MLPA and quantitative PCR. However such methods are labor-intensive and suffer from a variety of draw backs. In this month's issue Hegde et al. (see page 232) describe the development, validation and implementation of targeted CGH arrays for detecting single and multi-exon deletions and duplications in a variety of genes. Such a strategy can be readily adopted by clinical molecular laboratories and will likely, when coupled with robust sequence analysis, soon supersede other techniques due to high sensitivity, decreasing expense and versatility.



Enzyme replacement therapy and Fabry Disease

Enzyme replacement therapy has revolutionized the management of individuals with a variety of storage diseases. Fabry disease—a deficiency of α-galactosidase A—is no exception. The treatment of patients with recombinant enzyme results in dramatic improvement in the signs and symptoms of this disorder. However, enzyme replacement therapy is exceedingly expensive and not without some risk. Therefore, there is intense interest is determining whether lower than (now) standard doses might be efficacious in the long-term treatment of such disorders. In this month's issue Lubanda et al. (page 256) describe a study in which a lower dose of agalsidase β was employed following a standard therapeutic dose. The primary endpoint of this study was GL3 clearance and was achieved in 100% of patients with a 1mg/kg dose and was maintained in 90% of patients with a dose of 0.3mg/kg. A variety of other renal cell types were studied for GL3 reduction or clearance. The authors conclude that a lower dose of agalsidase β may be sufficient in some patients but not all. Future studies should address the long term clinical effects of transitioning to the lower dose and there will likely be intense interest in determining which patients may benefit from lower doses and which will continue to need standard doses. It will also be of interest to determine genetic and environmental factors that account for such differences.

News Briefs

Can you hear this painting?

Synesthesia is a well known condition in which individuals experience a mixing of their senses. People with this condition may, for example, see colors in response to sounds or vice-versa. This is not a metaphorical mixing of the senses but is an actual redirection of neural impulses resulting in sensory perceptions from crossed-stimuli. Well-known synesthetics include the artist Wassily Kandinsky, writer Vladimir Nabokov and physicist Richard Feynman. It is estimated that as many as 1% of people have the most recognizable form of this condition, and now researchers at the University of California, San Diego have performed a genome-wide scan on a 196 individuals from 43 families in which multiple members had synesthesia. Publishing in the February 2009 issue of *The American Journal of Human Genetics* (84;279-285) the authors found regions on chromosomes 2, 5, 6, and 12 that may be linked to this condition. In addition to the obvious novelty and titillating nature of this condition a deeper understanding of it could shed considerable light (sound?) on our perceptions of reality.

IFRD1

150 years after the description of Mendel's laws of inheritance, we have seen resounding success in applying them to a variety of human traits and diseases. However, we remain woefully ignorant of the mechanisms which underlie two hallmarks of inheritance, reduced penetrance and variable expressivity. In work by Asher et al. published in February in Nature Online (www.nature.com), a multi-institutional team has elucidated the role of *IFRD1* in modifying the course of cystic fibrosis. Mice with a deletion of *IFRD1* demonstrated significantly less inflammation and pulmonary damage following pulmonary infection with pseudomonas, the most common serious clinical pathogen in such patients. It appears *IFRD1* mediates its effect through the regulation of neutrophils and thus the inflammatory response. Thus, 20 years after the identification of the cystic fibrosis gene, this condition remains a workhorse of the genetics community continuing to help elucidate general principles of medical genetics.