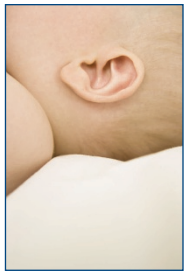
Highlights of This Issue

Bedside Genetic Testing in the Newborn Screening Context

Between one and three newborns per thousand have sensory neural deafness or are hard of hearing at birth. Identification of those infants prior to six months of age improves language outcomes and thus diagnosing deafness is a time-critical task. Bedside newborn hearing screening (NHS) is highly successful in identifying deaf or hard of hearing infants however such protocols have a high loss to follow-up. This month Schimmenti et al. (page 1006) report on a strategy which employs blood spot genetic testing for *GJB2* alleles as a means for rapid confirmation of the genetic etiology of hearing loss in a significant subset of infants who failed bedside newborn hearing screening. The authors analyzed 2,354 blood spots for common alleles in GJB2 and found that the prevalence of biallelic mutations referred by NHS programs was approximately one in 50. These findings demonstrate that when a newborn fails NHS there is a significant chance that *GJB2*-related hearing loss is present. Blood spot-based genetic testing for common *GJB2* alleles should be considered as second tier testing for bedside NHS and could conceivably be generalized to other genetic forms of hearing loss and other conditions.



Cis or Trans?

In autosomal recessive disorders determining whether sequence changes are in cis or trans is obviously vital to arriving at a correct molecular diagnosis. Allelic discrimination can be accomplished through the testing of family members but in reality this can be a cumbersome or even impossible task. Other techniques often depend on specific sequence changes for assay design and need extensive optimization. This month Chen & Schrivjer (page 1025) report the development of a method that does not fully depend on specific nucleotide changes to determine the allelic configuration of detected sequence findings. The investigators utilized digital PCR to separate and amplify alleles, employing subsequent Sanger sequencing to identify sequence changes. Their assay is a cost-effective method for allelic discrimination of short amplicons and was demonstrated in this publication through analysis of *GJB2* alleles. They also successfully developed a long-range digital PCR approach to determine the cis/trans relationships of mutations in the *CFTR* gene. This article points the way towards clinical implementation of determining allelic configuration of relatively common sequence changes.

News Briefs

Gene Patent Update – Supreme Court Bound?

The contentious issue of gene patenting continues to wind its way through the US court system. Early this year, Federal Judge Robert Sweet of the southern district of New York ruled that the Myriad patent claims on *BRCA1/2* were invalid, arguing in his opinion that genes are not legitimately patentable material. The crux of his argument, welcomed by much of the genetics community, was that as carriers of information genes perform the same role when isolated as they do in the body. Given that reality, Judge Sweet argued that claims relating to gene "isolation and purification" were irrelevant and invalid.

Myriad Genetics appealed to the Court of Appeals for the Federal Circuit, the appellate court that hears all patent cases in the US. In August that court issued a mixed decision, finding that genes are indeed patentable material, arguing that an isolated gene is a novel composition of matter. However, in an aspect of the decision often overlooked, they also argued that Myriad's claim to the association between mutations in *BRCA1/2* and an elevated risk of breast cancer (their so-called "methods claims") are not defensible.

The case has now been appealed to the US Supreme Court. The court will decide in the coming months whether they will chose to hear this case. Stay tuned.

Sorting out Complex Inheritance

In spite of progress in understanding the genetics of Crohn's disease, the topic remains confusing. Studying Crohn's disease has the potential for shedding insight not only into the underpinnings of this particular disorder, but could offer more general lessons for our appreciation of complex inheritance.

Towards these ends, we call your attention to a report published in this month's AJHG by Elding et al. Family studies for Crohn's disease report extensive linkage on chromosome 16q and have pinpointed *NOD2* as a possible causative locus. However, linkage is also observed in families who do not bear the most frequent *NOD2* causative mutations and no other signals on 16q have been found thus far in GWA studies. The authors sought to address the missing genetic contribution in Crohn's disease by applying a novel genetic mapping approach to GWA data from two large studies. This method takes into account the underlying structure of linkage disequilibrium (LD) by using genetic distances from LD maps and provides a location for the causal agent. Their investigation found evidence for genetic heterogeneity within the *NOD2* region and also showed an independent and previously unsuspected involvement of a neighboring gene, *CYL*.

These findings provide insight into the genetics of CD and suggest promising directions for understanding disease heterogeneity, with possible application towards understanding complex inheritance in general.