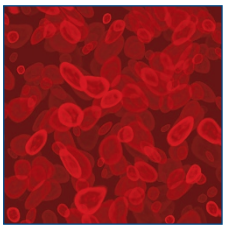
Highlights of This Issue

BRCA1/2 – Ordering the Right Test

Over 15 years out from the cloning of *BRCA1* and *BRCA2*, testing for mutations in these genes has become standard of care for a subset of patients who have specific indications. It is thus not surprising that larger and larger numbers of nongenetic specialists are ordering *BRCA* testing prompting concerns that the sometimes nuanced interpretation of results could prove problematic. This month we publish an intriguing article by Plon and colleagues (page 148) in which the authors studied the impact of different types of test results on clinical decision-making. Practicing physicians from five different specialties completed an online case-based survey and were asked to make genetic testing and management recommendations for the at-risk relatives of these hypothetical patients. When physicians were told that a patient carried a deleterious *BRCA1* mutation or a VUS 98% and 82% of physicians, respectively, recommended testing of at risk relatives. In both situations comprehensive *BRCA1/2* analysis was typically selected with a corresponding nine-fold increase in unnecessary genetic testing costs. Interestingly (and somewhat depressingly), there was no difference between physicians with or without prior *BRCA* testing experience. This study revealed that physicians chose more comprehensive testing for healthy relatives than current guidelines or logic would recommend, independent of their experience or specialty. The



authors conclude that reliance on genetic professionals as well as education of physicians has potential to improve the efficacy of testing and substantially reduce costs. In an accompanying letter to the editor a representative for Myriad Genetics responded to this study and discussed their efforts to minimize misinterpretation and inappropriate testing.

Making Sense of Alpha-Thalassemia

We are delighted to publish a review article this month that addresses the clinically important yet highly complex area of alpha-thalassemia (page 83). Alpha-thalassemia is prevalent in those world regions where malaria was (or is) epidemic. However, due to massive population migrations over the last hundred years alpha-thalassemia has become a relatively common clinical problem in other regions including North America and Australia. This disorder is highly heterogeneous at both the clinical and molecular level with both clinically unimportant carrier states as well as lethal hydrops fetalis in the case of hemoglobin Bart. Alpha-thalassemia is caused most frequently by deletions of the alpha genes and a very large number of alpha thal alleles have been described. However, clinical phenotypes and genotype-phenotype correlations have been only partly clarified to date. Readers will benefit from this clinically relevant and succinct distillation of an important and complex topic.

News Briefs

In honor of Valentine's Day this month, and the fact that many of you will be either giving or receiving chocolate, we bring news of the intersection of genetics and this most confection-oriented of holidays. The genome of the cacao tree, specifically *Theobroma cacao*, has been sequenced, yielding the (perhaps not unsurprising fact for us chocolate lovers) that chocolate is a more complex organism then we are - at least if one uses the number of genes as one's yardstick of complexity. The authors, publishing in *Nature Genetics* [www.nature.com] detail that the cacao tree contains over 28,000 genes. Many specific genes were identified which appear to be related to disease resistance, the production of cocoa butter, the unique aroma of chocolate as well as genes which contributed to its flavor and color. Importantly, for those of you, like me, who feel that chocolate is one of the few substances that makes life worth living, the particular variety of cacao tree which was sequenced produces an especially prized and delicious form of chocolate. The sequence of this particular tree is important since many cacao farmers are forced to grow trees that produce lower quality chocolate due to their greater disease resistance. It is therefore hoped that unlocking the genome of the "premium" cacao tree will lead to its more widespread cultivation. In this same issue of *Nature Genetics*, the genome of the woodland strawberry was also divulged. So as you tuck into that box of chocolates, or a chocolate-covered strawberry on Valentine's Day you can set a romantic mood by telling your loved one how many genes the chocolate genome contains. That's sure to get you some action.

Highlights of the *AJHG*

Nonsyndromic hearing loss is an intensely heterogenous disorder with etiologies ranging from the environment to genetics. On the genetic side, every form of inheritance has been documented with autosomal recessive (AR) inheritance being most frequent. To date, over 80 loci have been implicated in AR nonsyndromic hearing loss (NSHL) and causative mutations have been identified at over 30 of those loci. This month in *AJHG*, Borck et al. used homozygosity mapping in a consanguineous Pakistani family to detect linkage of ARNSHL to a 7.6 Mb region on chromosome 3q13.31-q21.1 within the previously reported DFNB42 locus. Sequencing of candidate genes in the region revealed a homozygous nonsense mutation in *ILDR1* as the cause of hearing impairment. Further analysis revealed 10 more families from the same geographical region with a variety of mutations in *ILDR1* as the cause of their ARNSHL. The *ILDR1* gene is highly conserved evolutionarily and expressed, as expected, in hair cell and supporting cell-containing neurosensory organs in the zebrafish ortholog ildr1. These data identify yet another gene found to underlie nonsyndromic prelingual sensorineural hearing impairment and add to our diagnostic armamentarium