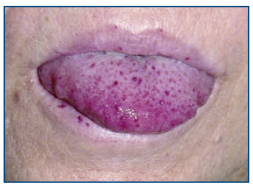
Highlights of This Issue

Hereditary Hemorrhagic Telangiectasia Review

This month we feature a GeneTest review which describes the diagnosis, management and pathogenesis of hereditary hemorrhagic telangiectasia or HHT (page 607). HHT is (at least in genetics terms) a relatively common disorder yet diagnosis is often delayed in part because one of its major features, nosebleeds, is relatively common in the general population. Moreover, a hallmark of the condition, telangiectasias on the lips, hands and oral mucosa, can be subtle. However, recognition and proper management of HHT is critical to avoiding profound morbidity and the potential for mortality. This review weaves together our knowledge of the molecular pathogenesis of HHT, its genetic heterogeneity and the implications for phenotype and management. At least five genes have been identified that result in HHT when mutated but two of these, *ENG* and *ACVRL1* (also referred to as *ELK1*) cause the significant majority of cases. Telangiectasias in the nasal mucosa, GI mucosa and brain (i.e. AVMs) generally present with hemorrhage due to the inappropriate connection between a high pressure arteriole and the venous system which is incapable of handling the higher pressures it is now subjected to. The complications that arise due to AVMs in the lungs and liver are generally not secondary to hemorrhage but rather to shunting of blood. Molecular genetic testing is quite useful in the setting of HHT both to confirm a diagnosis and also to establish the genetic subtype; something that has begun to influence care.



Predicting Fragile X Premature Ovarian Insufficiency

The complexities of fragile X mental retardation have been a constant within medical genetics now for several decades. This complexity has manifested in its unusual inheritance, anticipation and most recently in the recognition that pre-mutation carriers are prone to several important clinical risks. For women who carry an *FMR1* premutation, there is a significant risk for fragile X associated primary ovarian insufficiency or FXPOI. This is potentially extremely important for those carriers whose families and reproductive lives have already been significantly affected by their fragile X status. However, predicting at what point a woman might suffer premature ovarian failure is difficult. This month Spath et al (page 643) described an analysis of over 1000 women designed to identify those factors most associated with FXPOI. They found that the most significant parameters associated with this condition were the CGG repeat size and smoking. The authors develop a prediction model based on these two parameters and mean menopausal age of first-degree relatives to estimate the probability of FXPOI. This study represents a first step towards clinical application of FXPOI prediction.

News Briefs

Hail to the Chief

The prestigious Presidential Commission for the Study of Bioethical Issues advises the US President about issues stemming from advances in biomedicine, science and technology. The purpose of the commission is to ensure that scientific research, health care delivery, and technological innovation are conducted in an ethically responsible manner. The commission recently announced that its next focus will be on addressing the potential problems raised by the emergence of genome sequencing in clinical care and research. The working title of their effort will be "Genes to Genomes: Collection, Use and Governance of Human Genome Sequence Data"; a strong focus of their inquiry will be addressing the fact that we are rapidly accruing far more genetic information than we know how to interpret. The commission recognizes that we face challenges related to data protection, privacy, consent and counseling as we expand the use of next generation sequencing in research and begin to implement it in both the clinical and public health realms.

Highlights of the *AJHG* Pleiotropy and Disease

A fascinating study reported this month in the *AJHG* sheds light on the molecular etiology of geleophysic dysplasia (GD) and acromicric dysplasia (AD), while presenting conundrums regarding pleiotropy and disease manifestations. GD and AD belong to the acromelic dysplasia group and are both characterized by severe short stature, short extremities and stiff joints. *ADAMTSL2* mutations have previously been identified in a subset of GD patients but the molecular basis for AD has been unknown. In this report, the investigators, using exome sequencing, demonstrated that *FBN1*, the gene responsible for Marfan Syndrome, is also responsible for cases of both GD and AD. All of the 16 heterozygous mutations identified in 29 GD/AD cases were in exons 41-42 of *FBN1*, which encodes a TGF-binding protein-like domain 5 (TB5). The authors also demonstrated that there exists a direct interaction between *ADAMTSL2* and *FBN1*, implicating a disruption of this interaction as the underlying mechanism of GD/AD phenotypes. The investigators found no obvious differences in the nature of the mutations identified in GD compared to mutations identified in AD and it remains unclear why mutations affecting the TB5 domain of *FBN1* gave rise to GD/AD rather than Marfan syndrome. We clearly have much to learn about genotype/phenotype relationships, even in well studied disorders like Marfan syndrome.