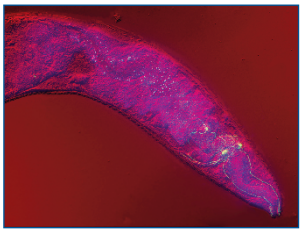
Highlights of This Issue

Interpreting Microarrays

We feature two important articles regarding chromosomal microarray (CMA) testing this month. Coulter at al., (page 770) explore how CMA testing influences medical management, performing a chart review of CMA testing during a 12 month period on patients with developmental disability, intellectual disability, autism spectrum disorder and congenital anomalies. Among 1,792 patients 13.1% had clinically relevant results. Clearly abnormal variants generated a recommendation for clinical action over 50% of the time and in about a third of patients with variants of possible significance clinical recommendations were forthcoming. This study documents the utility of CMA testing for patients with a broad range of phenotypes and substantiates that clinical recommendations follow from CMA testing in a high proportion of cases.

As we increasingly use CMA analysis we need ever more expansive data sets in order to effectively interpret complex results. A major step towards this goal is reported by Kaminsky et al. (page 777). This study represents the largest CNV case controlled study to date comprising over 15,000 cases and over 10,000 controls. The authors found 14 deletions and seven duplications to be significantly overrepresented in cases, providing a clinical diagnosis as pathogenic. These data begin to provide an evidence-base to guide clinicians across many disciplines involved in the diagnosis, management and care of patients and their families. Similar approaches will be needed as we grapple with the interpretation of whole genome sequencing.



Darwin would be proud – Worms in *GIM!*

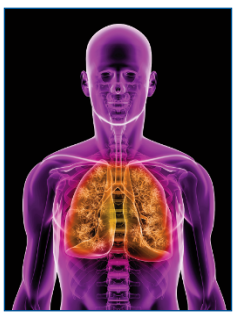
We publish *GIM's* first nematode paper this month. But rest assured, we maintain our strong clinical focus. A challenge confronting clinical laboratories is access to normal controls and samples with defined molecular abnormalities. This is a particularly difficult challenge in rare genetic diseases and highly complex disorders such as those affecting mitochondrial function. On page 794, Chen et al, investigate the use of *Caenorhabditis elegans* mitochondria as an aid to laboratories that perform mitochondrial respiratory chain complex assays. The results are intriguing and suggest the possible utility of nematode mitochondria as a tool to provide a virtually inexhaustible supply of mitochondria with defined effects for development of assays and as a potential source of control specimens.

If confirmed and extended, such samples could prove valuable to clinical laboratories. Finally, the results nicely illustrate the common descent of all organisms. It would appear that our mitochondria have changed little since the common ancestor of *C. elegans* and humans lived ~500 million years ago.

News Briefs

Genotype Specific Therapy for Cystic Fibrosis

21 years after the cloning of the Cystic Fibrosis Transmembrane Receptor (CFTR), detailed molecular knowledge of the genetic basis of this disease is resulting in progress towards treatment. Earlier this year a team led by Queen's University of Belfast, Northern Ireland, announced that a new drug specifically targets disease in those with a Celtic CFTR founder mutation (G551D). The drug, VX-770, directly targets CFTR, rendering it patent to chloride ions and partially correcting the underlying physiological defect. 161 subjects were randomized to receive either VX-770 or a placebo for one year. Those receiving active agent exhibited average improvement of ~20% in measures of lung function while those receiving placebo showed no change. Subjects receiving the active agent also demonstrated > 50% fewer pulmonary exacerbations requiring antibiotics and gained ~3 kilograms, suggesting possible improvement in GI function. Subjects showed a halving of sweat chloride concentrations, dramatic evidence of its molecular efficacy *in vivo*. VX-770 appears active against those with the G551D mutation, responsible for CF in about 5% of patients. Work is underway to build agents active against ΔF508, which would have a far greater impact due to that mutation's higher prevalence. Such progress reminds us of the long lag that we must expect between basic science discoveries and their practical impact – but also vindicates our confidence that the way forward in battling human disease is ultimately through research that illuminates basic mechanisms of biology and human disease



Highlights of the *AJHG* Leukodystrophies

The Leukodystrophies are a highly heterogeneous group of inherited neurodegenerative disorders characterized by abnormal white matter on brain imaging. 30%-40% of cases remain unexplained after extensive clinical investigation. This month in the *AJHG* Bernard et al., report that TACH (Tremor-Ataxia with Central Hypomyelination), a form of childhood-onset leukodystrophy results from mutations in the *POLR3A* gene that encodes the largest subunit of RNA polymerase III (Pol III). Linkage data, as well as overlapping clinical features, have suggested a relationship between TACH and two other leukodystorphies, Leukodystrophy with Oligodontia (LO) and 4H Syndrome (Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism). In total, 14 recessive mutations were found in 19 cases of either TACH, 4H or LO, establishing the allelic nature of these leukodystrophies.

Pol III has a wide set of target RNA transcripts, including all nuclear encoded tRNA, leading the authors to suggest that a decrease in POLR3A levels leads to dysregulation of the expression of certain Pol III targets with resultant altered cytoplasmic protein synthesis.