This Month in *The Journal*

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Distribution of mtDNA Heteroplasmy

Wonnapinij et al., page 582

The penetrance of diseases as a result of mutations in mitochondrial DNA (mtDNA) can be affected by the level of heteroplasmy, or the amount of mutated mtDNA in comparison to wild-type mtDNA, in a cell. Because it is known that mtDNA is maternally inherited, it might be expected that an individual's level of heteroplasmy would be the same as that of his or her mother, but that is not often the case. Heteroplasmy levels can differ significantly between mother and child, and that can contribute to problems when trying to predict disease risk in the child. A distribution of heteroplasmy in offspring is usually observed, and researchers have predicted the distribution on the basis of the expectation that the mean level of heteroplasmy in offspring should be equal to the level of heteroplasmy in the mother. Additionally, the variance of the levels could be predicted mathematically. Because these methods assume a normal distribution and, thus, have limitations at the extreme levels of heteroplasmy, Wonnapinij et al. describe how the application of an old theory can be used to effectively determine the entire heteroplasmy distribution. The authors use Motoo Kimura's theory of gene frequency probability to establish the heteroplasmy distribution in the presence of random genetic drift. By comparing the distributions observed experimentally in data from humans, mice, and *Drosophila* with those estimated by Kimura's theory, the authors demonstrate how well the Kimura methodology can predict the heteroplasmy distribution in offspring.

Mutations in *EYS* Cause RP

Collin et al., page 594

Although mutations in over 20 genes from a number of different gene families have been found to cause autosomal-recessive retinitis pigmentosa (arRP), it is estimated that about 70% of cases still do not yet have a known etiology. A large percentage of Spanish arRP cases have been linked to one RP locus, RP25, but although the candidate region has been narrowed, no causative gene variants have been found. Collin et al. use homozygosity mapping and candidate-gene screening to establish the cause of arRP in their patients. They first recognize that their locus coincides with RP25 and that five known genes reside in the region of overlap. One gene, *EGFL11*, is abundantly expressed in the retina, but initial sequencing of the gene does not reveal any potential disease-causing variants. In an effort to expand the candidates in the locus, the authors propose that the predicted gene sequences just centromeric to *EGFL11* are actually additional *EGFL11* exons. Experimental analysis confirms that *EGFL11* does contain additional domains and that it is the human ortholog of the *Drosophila* gene, *eys*, that was previously found to be crucial in photoreceptor development and morphology. Mutation analysis of these previously unidentified exons identifies two homozygous mutations in three arRP families.

The Human Phenotype Ontology

Robinson et al., page 610

Relationships between disease phentoypes are often correlated with relationships between the genes that are disrupted to cause those diseases. Because of this, information about gene networks and pathways can be collected about genes that are mutated in similar diseases, and, likewise, known interactions between genes can contribute to establishing a list of candidate genes for related phenotypes. Phentoypic information is currently maintained in the Online Mendelian Inheritance in Man (OMIM) database, but nonstandardization of the nomenclature used can make computational analysis of the data difficult. To create an effective phenotypic resource, Robinson et al. use a combination of computer programs and manual curation to mold the OMIM data into the Human Phenotype Ontology (HPO). The arrangement of the phenotypic terms in the HPO allows diseases to be compared on the basis of their features, and diseases that share more specific phenotypes are deemed to be more closely related than those that share more general features. The authors demonstrate the utility of the HPO by evaluating the relationship among diseases of certain known classes. They find that their results not only cluster in expected patterns, but also predict other strong connections. Robinson et al. also show that the ontology can be used clinically as a diagnostic tool by reporting how well the HPO can interpret clinical descriptions that lack specificity or completeness, characteristics of patient data that are often encountered.

Phoencian Male Genetic Lineages

Zalloua et al., page 633

The settlements and movements of the Phoenician civilization throughout the Mediterranean region have been quite well documented in historical writings and archeological

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studies. Zalloua et al. seek to contribute genetic data to this knowledge by identifying regions of the Y chromosome in modern populations that are most likely representative of Phoenician heritage. This task is complicated by the fact that a number of population expansions occurred in a similar pattern as that of the Phoenicians; the civilizations started in the lands east of the Mediterranean and grew toward the west. Therefore, just identifying gradients in the region is not sufficient, and the authors develop a method to distinguish the pattern of a specific population from that of the movements of other peoples in the same area. The authors' strategy is based on identifying paired locations that had different contact with the Phoenicians in correlation with physical distance from the source of the expansion. By analyzing the data from thousands of males in these chosen locations, Zalloua et al. are able to identify lineages that are likely to have been spread by the Phoenician civilization. In addition, they also learn more about the population movements in the Mediterranean region and propose that the methodology developed will contribute to further distinction of population expansions in regions where multiple civilizations overlapped.

TBX15 Mutations in Cousin Syndrome

Lausch et al., page 649

Development of genetically altered mice to model human disease is a common occurrence in today's research. Identification of human genetic deficiencies through the use of genetically modified mice is a less common, but equally powerful tool. Lausch et al. use their knowledge of *Tbx15* mutant mouse phenotypes to identify *TBX15* mutations as potentially causative of Cousin syndrome (pelviscapular dysplasia), a multifaceted congenic human disorder. The droopy-eared mouse, studied for more than four decades with no associated human disease, is known to be caused by functional null mutations in *Tbx15*. *Tbx15* is one member of the T-box gene family that encodes conserved transcription factors that share a common DNA-binding domain, the T-box. These transcription factors are involved in numerous developmental processes ranging from patterning to differentiation. Spontaneous and engineered mice harboring *Tbx15* mutations present with craniofacial defects, abnormal coat color patterning, small size, hypoplastic scapula, and other bone dysmorphogeneses. On the basis of the striking similarities between the phenotype of these mice and two patients with Cousin syndrome, these authors identify homozygous *TBX15* mutations in both patients, linking pelviscapular dysplasia to this gene and establishing the droopy-eared mouse as a model. This work will potentially lead to better disease diagnosis and may stimulate *TBX15* and other T-box genes to be tested as candidates in diseases with related phenotypes. Furthermore, this paper demonstrates the power of phenotype correlation in utilizing existing mouse strains to identify candidate human disease genes.