Introduction to evolutionary genomic approaches to human disease

This special edition of Applied & Translational Genomics, “Evolutionary Genomic Approaches to Human Disease”, provides 6 articles that span fundamental concepts, such as how natural selection, while generally increasing fitness, may simultaneously result in increased susceptibility to disease, evolution in mammalian development, placentation and birth processes, how comparative genomics can be used to identify cancer genes, and using microevolutionary signatures of population differences as a means to explain normal phenotypic variation and disease susceptibility. We have selected the presentation of these papers not only to exemplify the power of thinking in evolutionary terms about disease gene identification, but also, as evidence that past selection pressures in human may be at odds with current environmental exposures and behaviors and lead to what we in aggregate consider as common complex diseases such as obesity, hypertension and preterm birth.

Justin Fay provides an introductory platform for considering how “positive selection” for advantageous traits may carry with it negative consequences by reviewing genome-wide and gene-specific studies. He describes important recent evidence that reveals that adaptive variants are frequently linked to disease-causing hitchhiker alleles. Guangjun Zhang and colleagues describe how pathogenesis of human and animal cancers has been facilitated by evolutionary conservation of chromosomal relationships. They demonstrate approaches to and insights in oncogene discovery by investigating copy number alterations that are associated with specific types of cancers and recognizing homology of these changes across species. As the aneuploidy regions in any cancer harbor too many genes for causative assignment, comparison across species provides an efficient and effective filter.

Perhaps one of the greatest targets for natural selection and variation between species during evolution has been in reproduction and pregnancy-related genes. Evidence for divergence in reproduction-related genes was initially apparent with complete genome sequence reports of the human, chimpanzee and mouse, but remained underutilized as a pathway of disease gene discovery for common conditions such as prematurity, preeclampsia, and metabolic reprogramming (Developmental Origins of Health and Disease). In the first three manuscripts related to pregnancy and early development, Power and Schulkin describe how lactation served as a precursor to placental function and is maintained as a critical contributor to infant development. These authors go on to describe current concepts on how modern metabolic disease states may be contributed to mismatches between early in utero and early postnatal environment and later life nutrient states. Chuong et al. describe the wide variation in placental structure and function between mammals, the genomic changes that have engendered this evolution such as gene imprinting and strategic placement of endogenous retroviruses, and the disease states that may result from species specific adaptations. Stemple et al. perform an elegant phylogenetic analysis of the evolution of fetal membrane rupture (or lack of) during labor, and evaluate the molecular basis of this process by analyzing nonsynonymous nucleotide changes in connective tissue and related genes that are reflected with human variation at or near these replacement sites. As preterm premature rupture of membranes (PPROM) is a common cause of preterm birth, these polymorphisms provide logical candidates for PPROM risk in human association studies.

Finally, in a broad-sweeping approach for nonbiased selection of genes and specific variants that are involved in normal human trait variation as well as disease risk, Ge Zhang and colleagues propose a novel analytic approach comparing a measure of population difference in polymorphism frequencies (FST) with predicted evolutionary branch distance of existing geographic cohorts. By applying this measure to genome wide association data from several traits (e.g., height, serum lipid concentrations) or disease processes (e.g., obesity, diabetes), validation of this approach is demonstrated.

The reviews and new analytic papers comprising this special edition reflect the power incorporating evolutionary influences the genomic, developmental and physiological studies hold. We are committed at Applied and Translational Genomics to encouraging ongoing submissions in this area and look forward to comments from our readership about these manuscripts.