Genetics Select

Cell

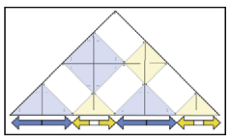
Faster, smaller, easier, and better—DNA sequencing technologies have improved by quantum leaps in the past decade. This Genetics Select highlights recent studies that demonstrate how these technological advances have greatly expanded the scope and power of human genetics, especially in the blossoming fields of personalized medicine and palaeogenetics.

Who Dat Ancestor?

Current sequencing technologies can easily extract genetic information from fossilized bone and hair. However, DNA degradation over time and contamination with modern human DNA has stymied efforts to sequence entire genomes of extinct humans. Now, Rasmussen et al. (2010) overcome these technical challenges to sequence the complete genome of a Saqqaq Eskimo man who lived in one of the first cultures in Greenland approximately 4000 years ago. Derived from a tuft of hair preserved in permafrost, the genome was remarkably intact, with <1% of the bases damaged by deamination. Further, an innovative decontamination protocol ensured that any DNA from modern Northern European scientists could easily be separated from the prehistoric DNA sequences. As a result, the authors recovered ~80% of the diploid genome and over 350,000 single-nucleotide polymorphisms (SNPs). These high-quality genomic data provided impressive personal details about the Palaeo-Eskimo man: he had brown eyes, dark skin, and blood type A(Rh+). His dark, thick hair had a tendency for balding, and his metabolism was adapted for cold weather. This study demonstrates that sequencing genomes from prehistoric humans not only is possible but also supplies new insights into the migration of ancient populations and biochemical characteristics of their people—information largely unattainable by traditional analyses of fossils. For example, a comparison of the Palaeo-Eskimo's SNPs with genomic data from modern humans suggests that the first Greenlanders probably crossed the Bering Strait independently of the ancestors of present-day Native Americans.

*M. Rasmussen et al. (2010). Nature **463**, 757–762.*

Artist reconstruction of the Palaeo-Eskimo man based on single-nucleotide polymorphism (SNP) analysis. Drawing by and courtesy of N. Gotfredsen.



Dot-plot analysis of the chimpanzee Y chromosome showing the tandem array of two massive palindromes. Image courtesy of J. Hughes and H. Skaletsky

Separating the Men from the Chimps

Six million years before the Saqqaq people separated from their North Asian ancestors, humans diverged from their closest living relatives, the chimpanzees. Despite the obvious phenotypic differences between chimpanzees and humans, our genomic sequences appear to differ by only 1%. Now, Hughes et al. (2010) report that the chimpanzee Y chromosome is surprisingly different from the human Y chromosome in both sequence and structure. Y chromosomes are challenging targets to sequence because they contain massive palindromes that are nearly perfect mirror images of each other. Using an interactive mapping method, the authors overcome this technical hurdle to produce a complete and accurate map of the chimpanzee Y chromosome, which they easily align with the existing map of the human Y chromosome. Remarkably, more than 30% of the chimpanzee Y chromosome lacks a detectable homologue in the human Y chromosome. In contrast, only 2% of chimpanzee autosomes are missing an equivalent sequence on their human autosome counterparts. In addition, the chimpanzee Y chromosome contains only two-thirds of the number of gene families found on the human Y chromosome, and the homologous sections that are present in both species have undergone substantial rearrangements. These results contrast sharply with the prevailing view that Y chromosomes evolve by simple gene loss that slows down over time. Why have the human and chimpanzee Y chromosomes diverged so quickly compared to the autosomal chromosomes? Sperm competition in chimpanzees is especially fierce because several male chimpanzees mate with one female during each reproductive cycle. The authors speculate that the intense sperm competition in chimpanzees combined with the rapid kinetics of recombination in Y chromosomes have resulted in the dramatic remodeling of this small sex chromosome over the last six million years.

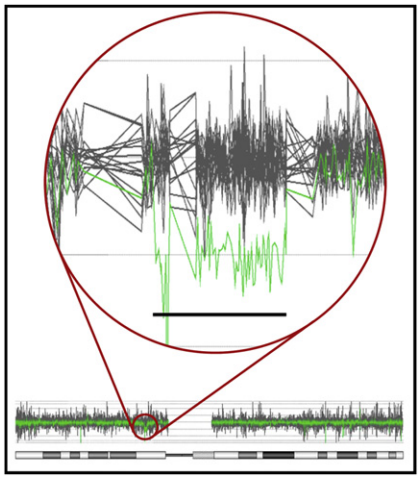
*J.F. Hughes et al. (2010). Nature **463**, 536–539.*

Let's Talk Man to Man

Although the sequence variation between the chimpanzee and human Y chromosomes exceeds theoretical predictions, a new study by Rozen et al. (2009) indicates that the sequence diversity of the Y chromosome across modern men is probably lower than expected. The Y chromosome contains genes "left over" after the X and Y chromosomes diverged, called X-degenerate genes. The authors sequenced 16 of these X-degenerate genes in 105 men from diverse genetic backgrounds.

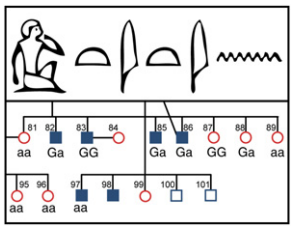
Surprisingly, they could detect only 126 unique nucleotide variants in the X-degenerate genes, and only 12 of these variations actually alter the protein sequence. Thus, across the 105 men examined, the X-degenerate proteins encoded by the Y chromosome differ on average by only 0.89 residues per chromosome, and half of this protein diversity arises from only one specific aspartate to glutamate substitution. The authors conclude that the X-degenerate genes on the human Y chromosome have changed very little over the last 100,000 years. For fans of the Y chromosome, this sequence stabilization is good news. Known to incur dramatic gene loss over the last 200 million years, the Y chromosome is predicted by some geneticists to disappear completely in the next ten million years. Now, these new sequencing results by Rozen et al. uncover an evolutionary pressure on the Y chromosome that may prevent this rapid decay and help to preserve this small chromosome.
S. Rozen et al. (2009). Am. J. Hum. Genet. ***85,*** *923–928.*

Rare Losses Cause Big Gains



Detection of a deletion on chromosome 16p11.2 by microarray comparative genome hybridization. Image courtesy of A. de Smith and R.G. Walters.

Gene deletions may eventually lead to the demise of the human Y chromosome in the next ten million years, but another type of gene deletion may be contributing to the present day obesity epidemic. Independent studies by Bochukova et al. (2010) and Walters et al. (2010) now report significant associations between heritable forms of obesity in humans and two different rare deletions on chromosome 16 (16p11.2). Interestingly, the 220 kb lesion identified by Bochukova et al. encompasses the *SH2B1* gene, which encodes a protein known to be involved in leptin and insulin signaling. On the other hand, Walters et al. found 15 families in which an obese child inherited a 700 kb deletion from an obese parent. Further, all obese first-degree relatives that were characterized also carried the same deletion. The overall frequency of the two deletions in obese populations suggests that together they cause ~1% of all morbid obesity cases world-wide. Although previous studies had identified numerous SNPs associated with obesity, these common variations account for only a small percentage of the total heritable component of the disease. Thus, both groups hypothesized that rare chromosomal variants, which are not picked up by traditional studies, may provide the missing genetic components underlying obesity. To increase their chances of finding these rare disease-causing alleles, both groups included in their initial studies obese individuals with cognitive deficits, who are known to harbor significantly more chromosomal deletions than individuals with normal cognitive ability. They then confirmed the relevance of the specific deletions in follow-up studies on obese individuals without the cognitive abnormalities. This two-step strategy appears to be a promising approach for identifying rare but important disease-contributing variants. Together, these studies provide data that challenge the popular hypothesis that common, interacting disease alleles underlie widespread diseases, such as obesity.
E.G. Bochukova et al. (2010). Nature ***463****, 666–670.*
R.G. Walters et al. (2010). Nature ***463****, 671–675.*



Ancient Egyptian hieroglyph for the verb "to stutter" (top) and a portion of the genetic pedigree used to map stuttering genes (bottom). Image courtesy of D. Drayna.

Sticky Speech

The speech disorder of stuttering and stammering may not be as prevalent as obesity, but it still burdens ~60 million people worldwide. Like obesity, stuttering is a heritable disease shaped by numerous environmental factors, making it extremely difficult to pinpoint specific mutations underlying the disorder. Now, Kang et al. (2010) identify multiple mutations that are significantly associated with stuttering in cohorts of South Asian and European descent. Interestingly, all of these mutations occur in genes that are involved in the correct targeting of enzymes to cellular organelles called lysosomes. Focusing initially on one large Pakistani family in which many individuals are affected by stuttering, the authors narrowed down the disease-associated locus to a 10 Mb region on chromosome 12q. Extensive sequencing of this region uncovered many variants that cosegregated with the disease. Most of these alleles were frequently present in unaffected individuals, except for one variant that encoded a lysine to glutamic acid substitution in the highly conserved GlcNAc-phosphotransferase enzyme. This protein adds a phosphate group to the N-linked oligosaccharides on enzymes destined for lysosomes, and deficiencies in the activity of these enzymes cause rare lysosomal storage disorders. Further analysis of genes governing lysosome metabolism identified six more mutations that are associated with stuttering in Asian and European populations. Although these mutations account for only a small percentage of stuttering cases worldwide, their connection to lysosomal enzymes provides a new starting point for probing the molecular mechanisms underlying this complex behavioral disease.
C. Kang et al. (2010). New Eng. J. Med. Published online February 10, 2010. 10.1056/nejmao0902630.

Michaeleen Doucleff