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'SATIABLE CURIOSITY: GENE CONVERSION ON THE Y CHROMOSOME

Author(s): Ann Turner

'SATIABLE CURIOSITY

Gene Conversion on the Y Chromosome

'Satiable Curiosity **is a column dedicated to the proposition that genetic genealogists are an untapped resource for resolving questions about DNA behavior -- how DNA changes over the course of a few or many generations and how DNA patterns are distributed around the world. Some questions are so broad that it could take decades to arrive at a conclusion, yet others are narrow enough to answer in a shorter time frame, perhaps even within a semester or two for a student research project. The results may nonetheless be of considerable genealogical utility and scientific interest, worthy of publication in a technical journal.**

The human Y chromosome has long stretches of duplicated segments, with multiple copies of some genes and genetic markers. These segments differ only slightly over most of their length, but microsatellites (Short Tandem Repeats or STRs) contained within these segments tend to be more variable, due to their relatively high mutation rate. Genetic genealogists take advantage of this variability when testing the multi-copy markers DYS385a/b, DYS459a/b, DYS464a/b/c/d, YCAIIa/b, and CDYa/b.

Although these duplicated segments vastly complicated the task of sequencing the Y chromosome, a stunning picture finally emerged.[1] The duplicated segments were not merely backup copies scattered along the length of the chromosome. The DNA sequences formed palindromes, with one copy reading the same as the other copy backward. By forming a hairpin turn, the copies could interact with each other during duplication of the Y chromosome, much like the paired autosomal chromosomes line up with each other and recombine.
Routine testing cannot distinguish the position of the copies, whether the "a" or "b" copy is closer to the centromere (diagrammed in Figure 1 as a narrow waist on the chromosome). Results are simply given in ascending order. Typical results for the markers listed above are 11-14, 9-10, 15-15-17-17, 19-23 and 37-38

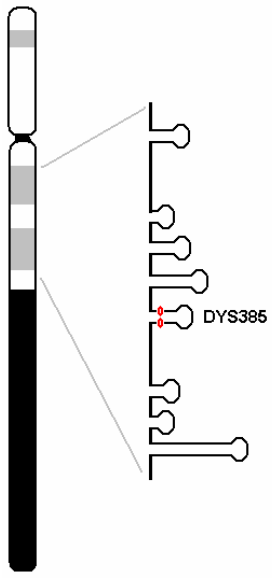

Figure 1.[2] Location of palindromes on the Y chromosome, numbered 1 to 8 starting at the bottom. DYS385a/b is on palindrome 4.

[1] Skaletsky H et al, "The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes," 2003, *Nature* 423:825-37

[2] Figure adapted from Graves JAM, "The degenerate Y chromosome – can conversion save it?" 2004, *Reproduction, Fertility and Development* 16:527-534

for R1b, the most common European haplogroup. The vast majority of mutations are single-step changes, so that an 11-14 result for DYS385a/b in an ancestor might change to 12-14 or 11-13 for a few descendants. That is counted as a "genetic distance" of one.

However, occasionally one line of descendants may exhibit a bigger jump, and 11-14 becomes 11-11 or 14-14. Does that mean that three single-step changes occurred on that one marker in that line? That would be a rare coincidence. Or is there another process at work? Gene conversion, where the sequence on one arm of the palindrome overwrites the sequence on the other arm, is a plausible explanation for the change to a "homozygous" state, where both alleles are the same.

The usual rule of thumb for relatedness would count such a change as three distinct events, making it appear that two people are not as related as they thought they were. It would be useful for genealogists to know if a single event accounted for the big change. Geneticists also have some curiosity: how long a stretch of DNA is involved in a gene conversion?[3]

Geneticists are obliged to use indirect means of estimating the length, but genetic genealogists could furnish them with cases where a gene conversion event occurred in one line of descent. Using a heterozygous sample and DYS385 as an anchor, sequencing could proceed in both directions until a few single nucleotide polymorphisms (SNPs) were encountered on the two arms of the palindrome. These SNPs could then be tested in the samples homozygous for DYS385. SNPs nearest to DYS385 might also be homozygous, but more distant SNPs might be heterozygous. The length of the gene conversion event could thus be bracketed.

DYS385 is a prime candidate for such an experiment, since a SNP is already known to exist nearby, the basis for the specialized Kittler protocol to distinguish the "a" and "b" copies.[4] However, the same process could be extended to other multi-copy markers, perhaps locating some SNPs which could be used to identify the location of the copies on the palindromes. The outcome of this experiment would be intriguing for geneticists as well as genetic genealogists.

[3] Bosch E et al, "Dynamics of a Human Interparalog Gene Conversion Hotspot," 2004, *Genome Research* 14:835-844

[4] Kittler R et al, "Apparent intrachromosomal exchange on the human Y chromosome explained by population history," 2003, *European Journal of Human Genetics* 11:304-14.

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