Sex
Chromosome Evolution & Medicine
Sex Chromosome Evolution: Y as Rotting X

A pair of autosomes → X Y → X Y → X Y
“The Y chromosome is particularly vulnerable … because it is not a matching partner for the X chromosome, so it cannot retrieve lost genetic information by recombination.”

“At the present rate of decay, the Y chromosome will self-destruct in around 10 million years.”
The Human Y Chromosome

The Y differs from other nuclear chromosomes:
- specific to one sex
- no crossing over
Old and new understandings of the human Y

- genetic wasteland
- merely a rotting copy of an ancient autosome
- full of junky repeats
- no productive recombination → all genes disintegrating
- headed for extinction
- no medical significance

~76 protein-coding genes → 27 distinct proteins; spermatogenic specialization

- many genes imported (from autosomes and X) during primate evolution; gene amplification
- gene-rich palindromes of unprecedented scale & precision
- gene conversion → better maintenance of genes in pairs?
- even single-copy genes preserved through natural selection
- spermatogenic failure, testis cancer & Turner syndrome

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Structure of a Y palindrome

- up to 1.45 million bp
- 99.94 - 99.997 % identity
- 1 or more testis genes
- < 0.06 % divergence

Palindromes comprise 25% of Y euchromatin and carry all intact copies of the long arm’s testis-specific gene families.

Knowledge of the Y’s hall of mirrors led to predictions, fulfilled, of structural variation with medical consequence.
Speculative prediction: palindrome - palindrome crossover yields mirror-image Y, an isodicentric chromosome
Isodicentric Y chromosomes confirmed by fluorescence in situ hybridization

Lange et al., Cell (2009)
Reexamined Y chromosomes and phenotypes of 2,380 patients studied for any of three reasons:

1. Discordance between sex chromosome constitution and anatomy

2. Microscopically detectable anomaly of Y chromosome

3. Men with little or no sperm production
Identified 60 patients with idicY or isoY chromosomes

51 of these arose through crossing over at palindromes

8 different Y palindromes “hit” (targets for crossing over)

A significant cause of spermatogonogenic failure in men

However, 20 of these patients were anatomically feminized

2 patients: SRY not present on idicY chromosome

18 patients: SRY present in two copies on idicY

Lange et al., Cell (2009)
Hypothesis…

Mitotic instability of idicY chromosomes --> XO cells in embryonic gonad --> feminization of external genitalia

Prediction…

The greater the distance between the centromeres, the greater the mitotic instability of the idicY, the higher the probability of anatomic feminization
Anatomically feminized (n=18)

Anatomically male (n=40)

Intercentromeric distance (Mb) 0 10 20 30 60 90

In human beings with idicY chromosomes, more Y DNA $\rightarrow$ greater likelihood of feminization

Lange et al., Cell (2009)
Speculations arising…

Could mitotic instability of idicY chromosomes be a significant cause of XO state in girls & women with Turner syndrome?

(No maternal age effect in XO Turner syndrome, unlike trisomy 21)

(In 3/4 of XO girls and women, the X chromosome is of maternal origin)

Could Y palindrome-palindrome recombination be a significant cause of Turner syndrome?
How to sequence a large palindrome whose arms are more similar than alleles?

- Allelic differences confound assembly, so avoid them by sequencing one and only one chromosome.
- Left vs right arms differ by only occasional nucleotide substitutions, so capture a few such differences in large-insert clones (e.g., BACs) derived from one man.
- Use these left-vs-right nucleotide substitutions as “unique markers” with which to grow BAC contigs, finding additional such markers as you iterate.
- HIMS: Haploid iterative mapping and sequencing.
Two Y chromosome BACs from one man

The BACs derive from opposite arms of a palindrome

11 nucleotide substitutions
99.99% identity
“Structurally complex genomic regions, which are known to have a role in human disease (Stankiewicz & Lupski, *Annu Rev Med*, 2010), remain inherently difficult to sequence, even with the new DNA sequencing technologies. Additional technological improvements (for example, much longer read lengths) are needed to sequence such complex regions ....”
“One of the key impediments in resolving the complexity of these regions is the diploid and polymorphic nature of the human genome. In the past, the distinction between allelic versus polymorphic variation has been successfully circumvented by the use of genetic material of haploid complexity.”

“The final sequence and assembly of the Y chromosome (which is unusually enriched for segmental duplications) was achieved in large part due to the fact that all the ‘BAC clones [came] from one man’s Y chromosome’ (Kuroda-Kawaguchi et al 2001). Sequence assembly was therefore not impaired by polymorphism and all sequence variants represented distinct copies of paralogous sequences.”
Proposal: Scrutinize 160 “structurally complex” euchromatic sites on X and autosomes by haploid iterative mapping & sequencing.