Sex Chromosome Evolution & Medicine

Sex Chromosome Evolution: Y as Rotting X


A pair of autosomes — X Y — SRY — X Y — SRY — X Y — SRY
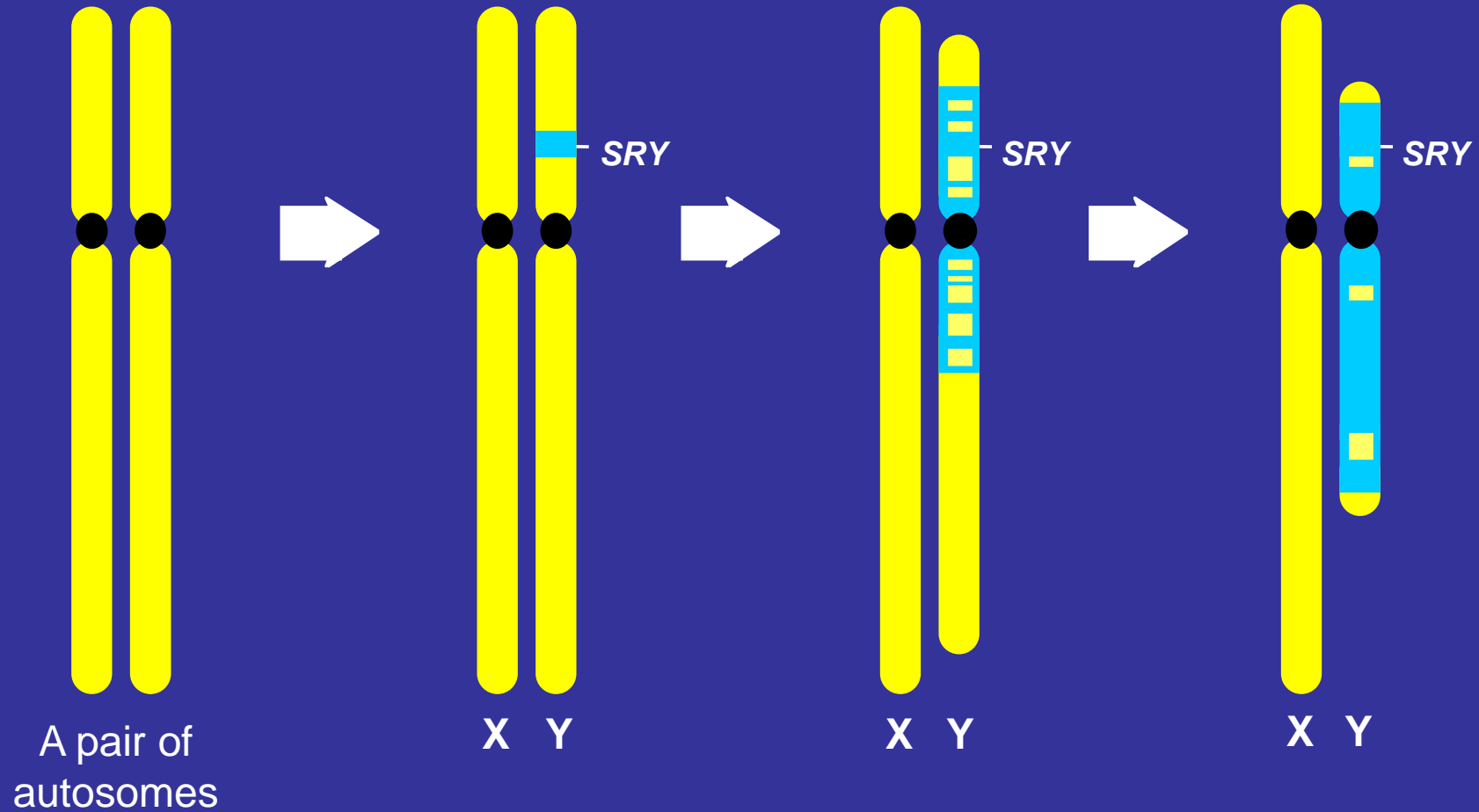
The future of sex

R. John Aitken and
Jennifer A. Marshal Graves

"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

Euchromatin
23 Mb ≈ 1% of human genome

Heterochromatin

p   q
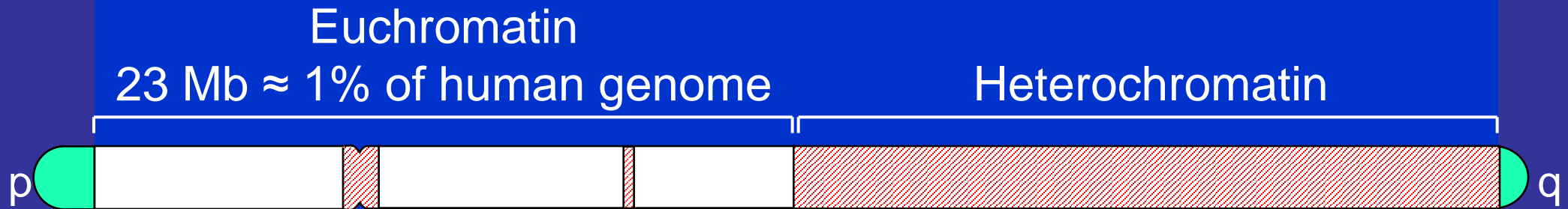
The Y differs from other nuclear chromosomes:

--specific to one sex

--no crossing over

Old and new understandings of the human Y

genetic wasteland

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

merely a rotting copy of
an ancient autosome

many genes imported (from
autosomes and X) during primate
evolution; gene amplification

full of junky repeats

gene-rich palindromes of
unprecedented scale & precision

no productive recombination
→ all genes disintegrating

gene conversion → better
maintenance of genes in pairs?

headed for extinction

even single-copy genes
preserved through natural selection

no medical significance

spermatogenic failure,
testis cancer & Turner syndrome

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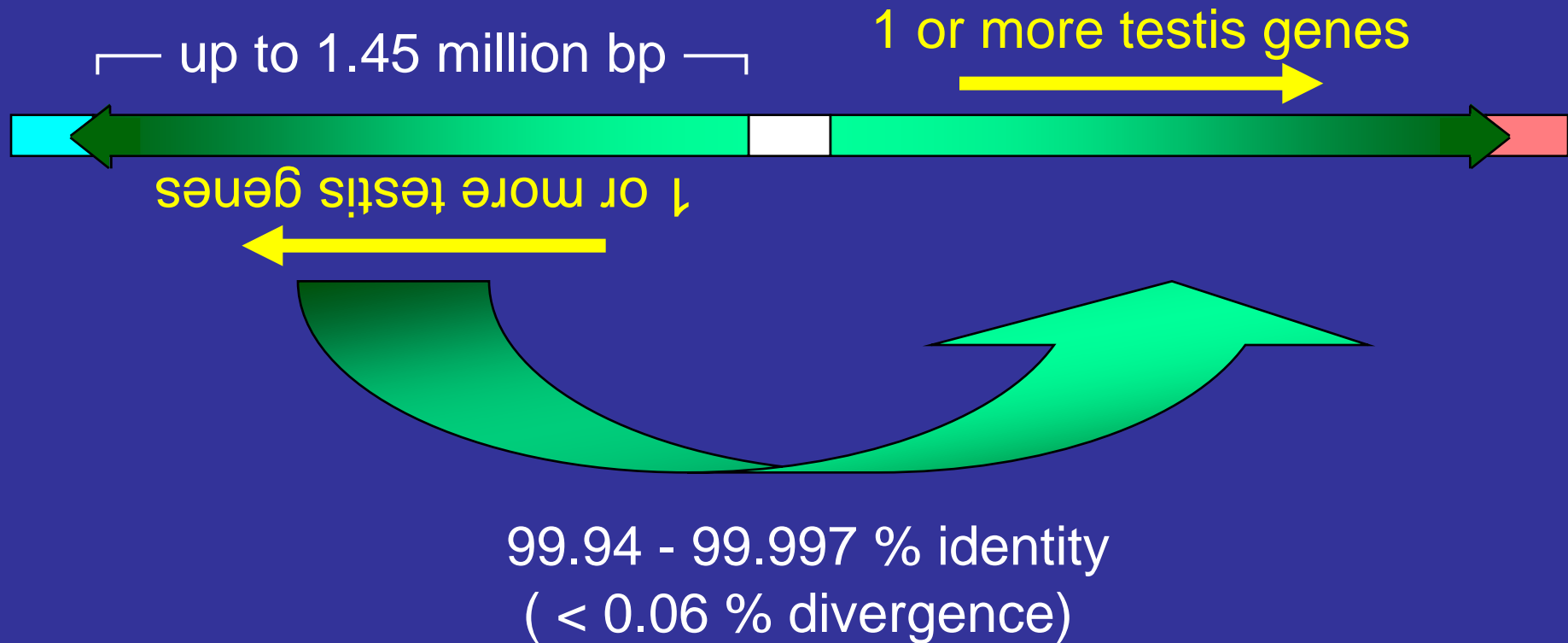maintenance of genes in pairs?

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Structure of a Y palindrome

up to 1.45 million bp

1 or more testis genes

1 or more testis genes

99.94 - 99.997 % identity
(< 0.06 % divergence)

Kuroda-Kawachuchi *et al.*, *Nature Genet.* (2001)

Skaletsky *et al.*, *Nature* (2003)

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

Yp   Yq

VCY
XKRY
HSFY
RBMY
PRY
CDY
BPY2
DAZ
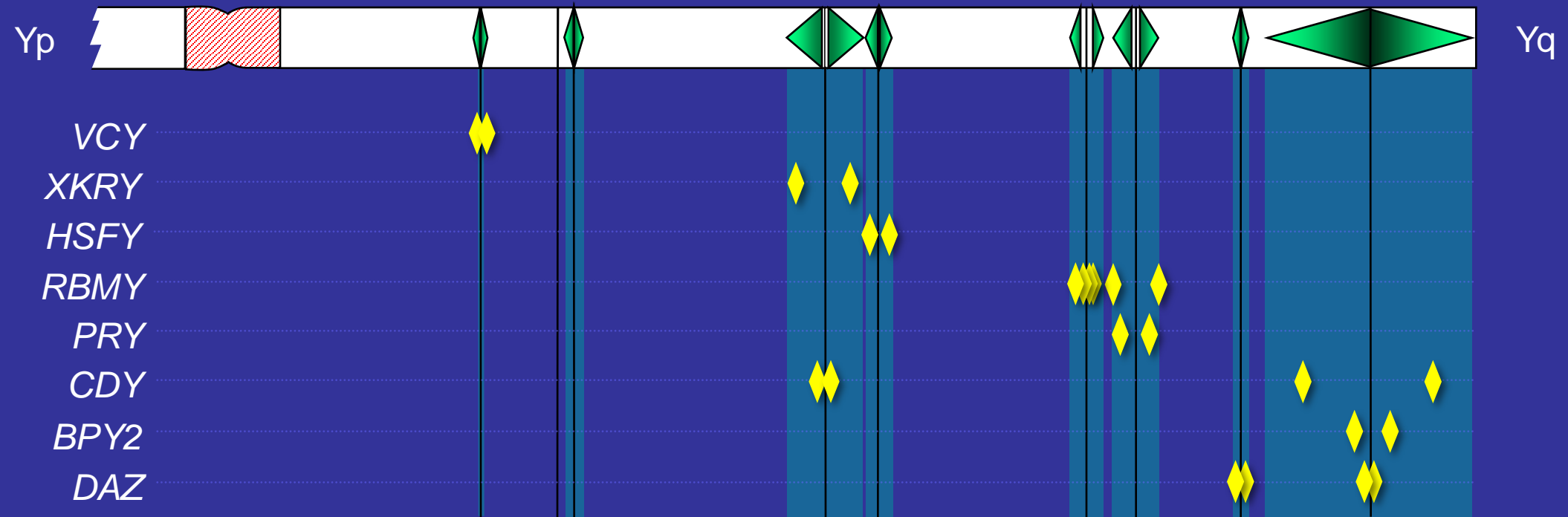
Knowledge of the Y's hall of mirrors led to predictions, fulfilled, of structural variation with medical consequence

Speculative prediction: palindrome - palindrome crossover yields mirror-image Y, an isodicentric chromosome
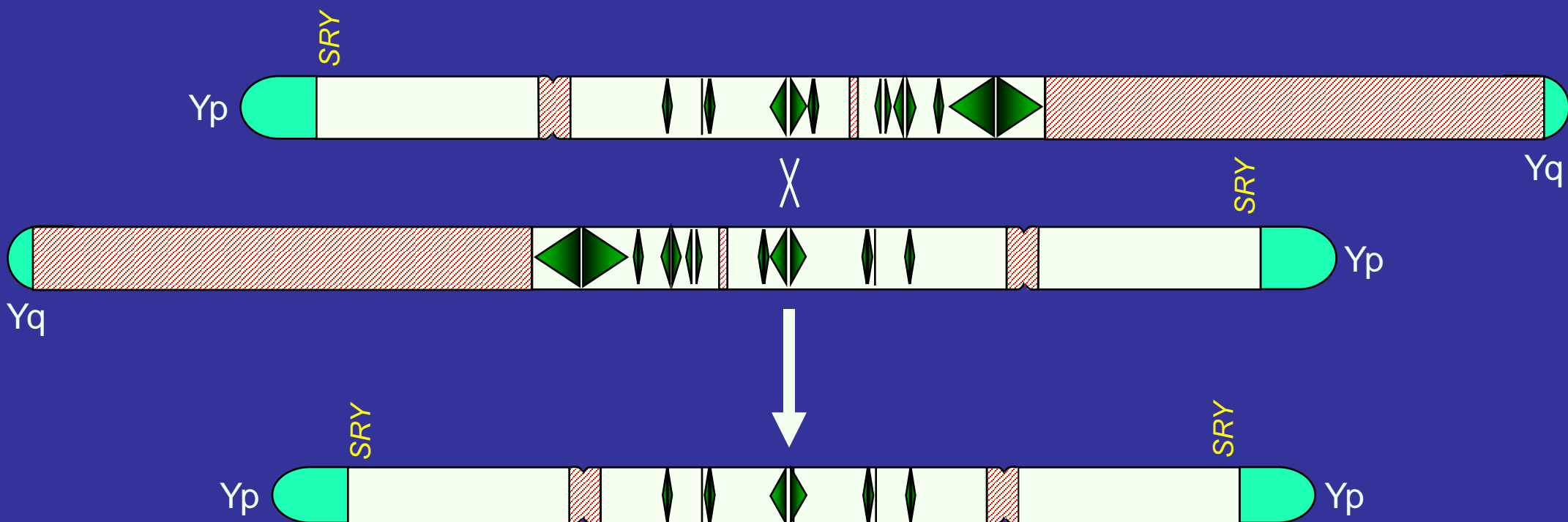
Isodicentric Y chromosomes confirmed by fluorescence in situ hybridization

normal chromosome

Yp .... Yq

Yp .... Yp

Yp .... Yp

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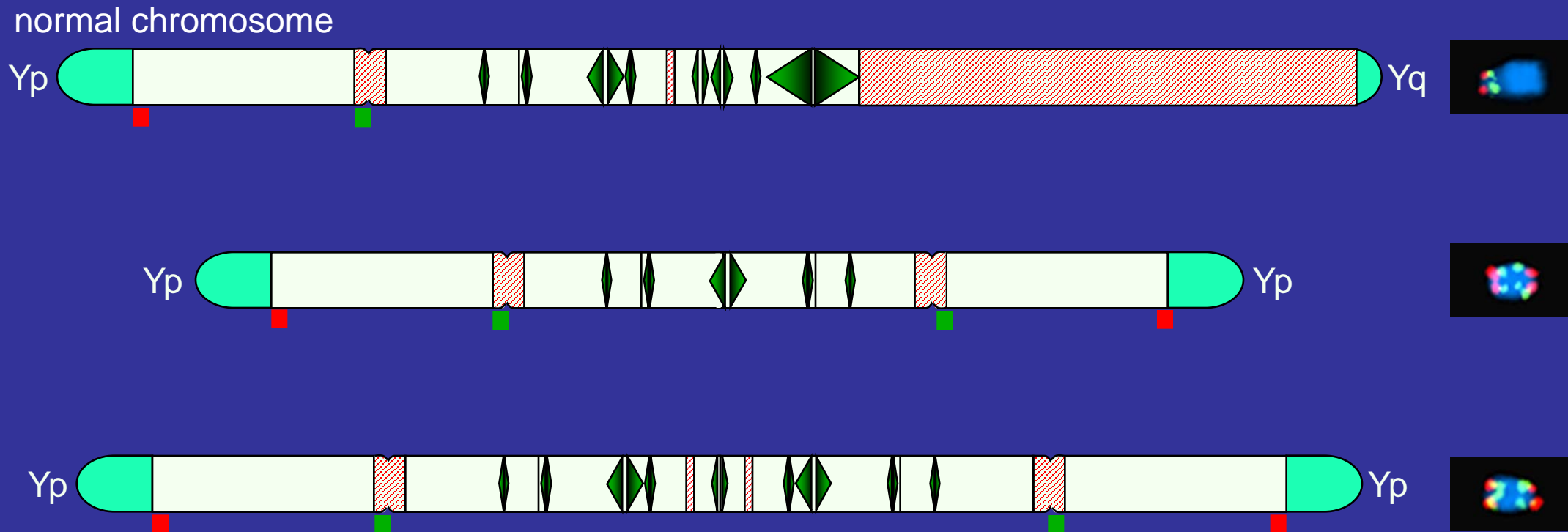
*Reexamined Y chromosomes
and phenotypes of 2,380 patients
studied for any of three reasons:*

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 spermatogenic 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

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

Correlation between sexual development & location
of targeted palindrome (distance between centromeres)
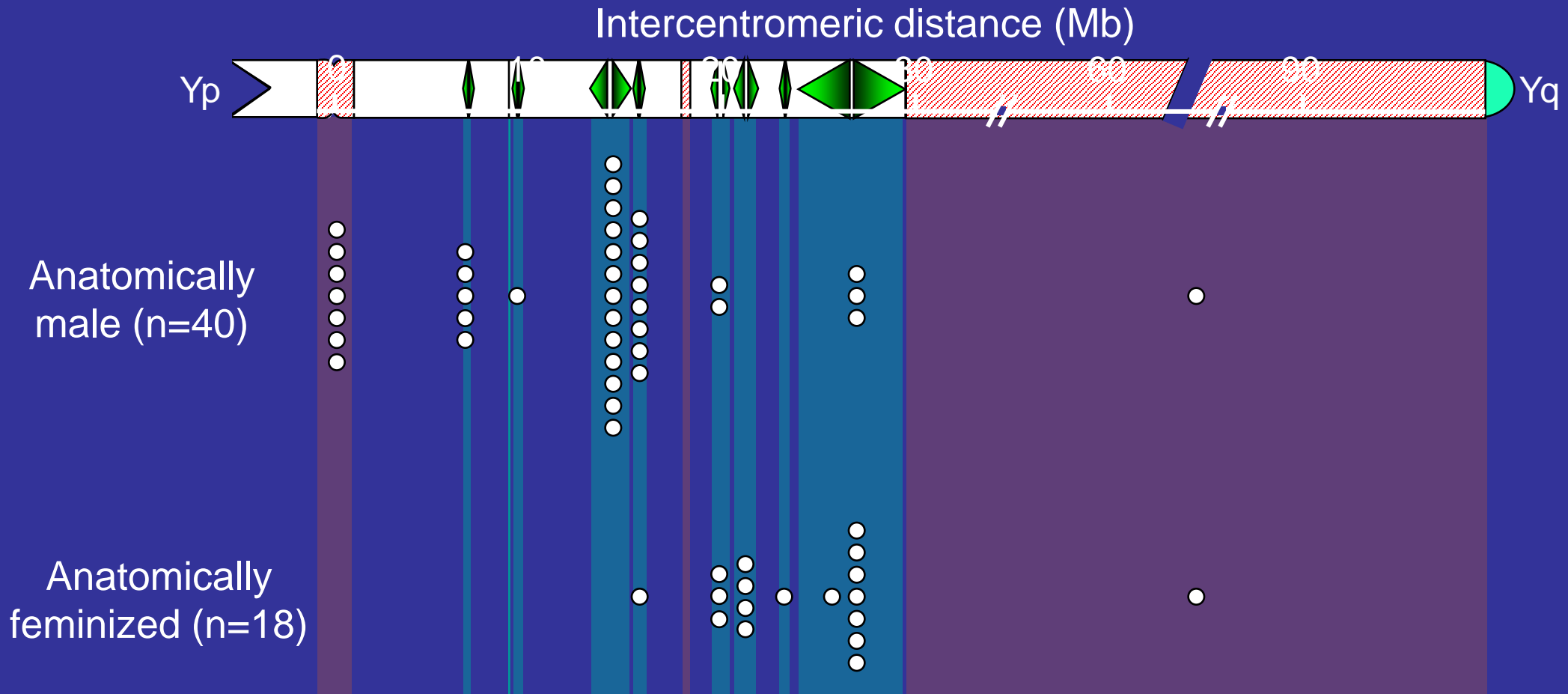
Lange *et al.*, *Cell* (2009)

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)

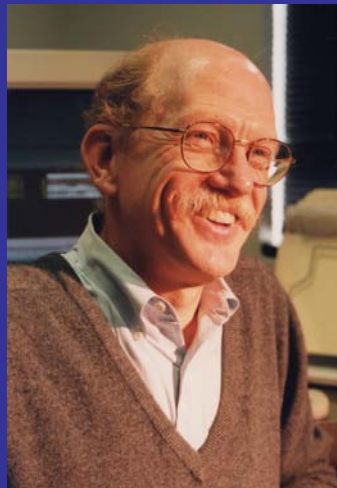(In 3/4 of XO girls and women, the X chromosome is of maternal origin)

Could Y palindrome-palindrome recombination be a significant cause of Turner syndrome?

Tomoko Kuroda-Kawaguchi
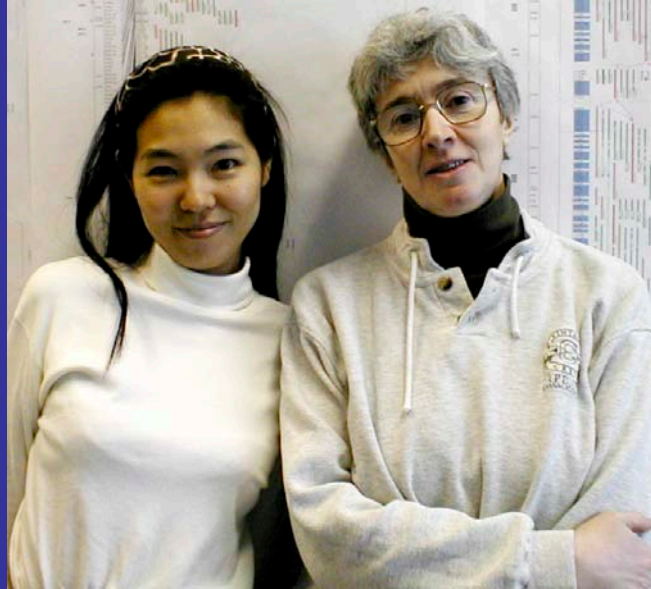
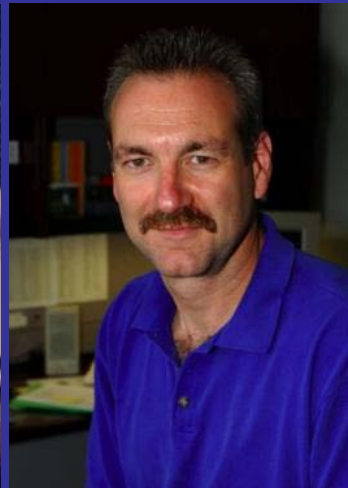Helen Skaletsky

Bob Waterston

Rick Wilson

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

RP11-157F24
161 kb

*** **** * * * *

105 kb overlap

178 kb
RP11-529I21

11 nucleotide substitutions
99.99% identity

The BACs derive from opposite arms of a palindrome

RP11-157F24   RP11-529I21

Charting a course for genomic medicine from base pairs to bedside

Eric D Green, Mark S Guyer & NHGRI

"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 ...."

Re: Proposal for Construction of a Human Haploid BAC library from
        Hydatidiform Mole Material

Date: Oct. 10, 2002

From: Evan Eichler, Case Western Reserve University
        Urvashi Surti, University of Pittsburgh
        Roel Ophoff, UCLA

"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