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# Intrachromosomal homologous recombination between inverted amplicons on opposing Y-chromosome arms

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ABSTRACT

Amplicons – large, nearly identical repeats in direct or inverted orientation – are abundant in the male-specific region of the human Y chromosome (MSY) and provide targets for intrachromosomal non-allelic homologous recombination (NAHR). Thus far, NAHR events resulting in deletions, duplications, inversions, or isodicentric chromosomes have been reported only for amplicon pairs located exclusively on the short arm (Yp) or the long arm (Yq). Here we report our finding of four men with Y chromosomes that evidently formed by intrachromosomal NAHR between inverted repeat pairs comprising one amplicon on Yp and one amplicon on Yq. In two men with spermatogenic failure, sister-chromatid crossing-over resulted in pseudoisoYp chromosome formation and loss of distal Yq. In two men with normal spermatogenesis, intrachromatid crossing-over generated pericentric inversions. These findings highlight the recombinogenic nature of the MSY, as intrachromosomal NAHR occurs for nearly all Y-chromosome amplicon pairs, even those located on opposing chromosome arms.



## 1. Introduction

The male-specific region of the human Y chromosome (MSY) contains many amplicons – large, nearly identical repeats – whose sequence similarity is maintained by gene conversion [1,2]. These long segments of high sequence identity render the Y chromosome susceptible to intrachromosomal homologous recombination that can result in interstitial deletions, duplications, inversions, or isodicentric chromosomes [3–13]. Interstitial Y deletions and isodicentric Y chromosomes are associated with a wide range of sex disorders, including male infertility, Turner syndrome, and sex reversal (reviewed in [14]).

Whereas each of the intrachromosomal homologous recombination events reported to date involve amplicons located on the same Y-chromosome arm, the reference Y chromosome also contains two sets of inverted repeats (IRs) that are composed of one amplicon on the short arm (Yp) and one amplicon on the long arm (Yq), namely IR1 and IR4 [1]. IR1 is composed of two amplicons that share >99% sequence identity over ~62 kilobases (kb), and IR4 is composed of two amplicons that share ~94% sequence identity over ~303 kb. Of note, the IR1 repeat on Yq is located within the *azoospermia factor c* (*AZFc*) region that contains genes essential for spermatogenesis and is almost entirely ampliconic [6].

We hypothesized that intrachromosomal homologous recombination between amplicons of IR1 or between amplicons of IR4 can generate two types of rearrangements: pseudoisochromosomes, in which the two chromosome ends are identical and in mirror-image orientation, and pericentric inversions (Fig. 1). For example, resolution of a double-strand break (DSB) in the Yq copy of IR1 by inter-sister-chromatid crossing-over with the Yp copy would produce a pseudoisoYp chromosome, which carries a partial duplication of Yp and a partial deletion of Yq, and a pseudoisoYq chromosome, which carries a partial duplication of Yq and partial deletion of Yp. Transmission of the former would likely result in a male offspring with impaired spermatogenesis due to the absence of multiple genes from the *AZFc* region. Alternatively, resolution

*Abbreviations:* MSY, male-specific region of the Y chromosome; NAHR, non-allelic homologous recombination; *AZFc*, *azoospermia factor c*; IR, inverted repeat; DSB, double-strand break; STS, sequence-tagged site; FISH, fluorescence in situ hybridization; PAR, pseudoautosomal region.

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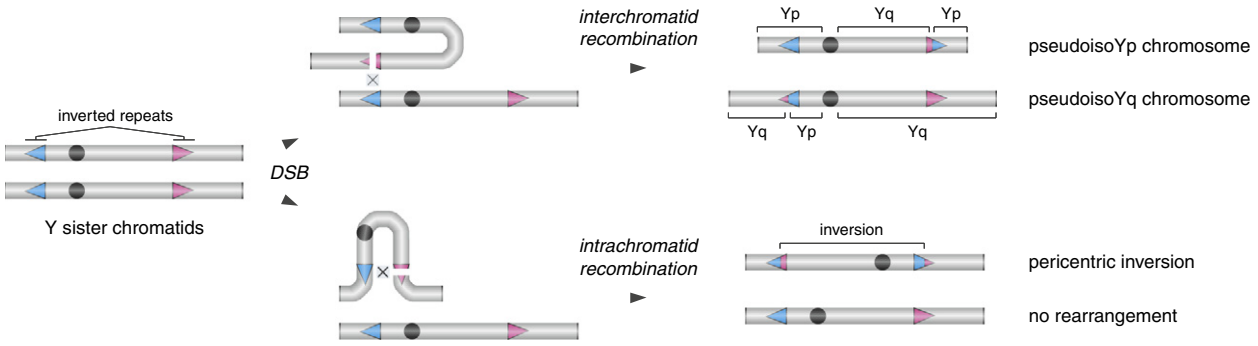


**Fig. 1.** Mechanisms of pseudoisochromosome formation and pericentric inversion. Ectopic homologous recombination between inverted repeats composed of one amplicon on the short arm (Yp) and one amplicon on the long arm (Yq): crossing-over between sister chromatids generates pseudoisochromosomes, intrachromatid crossing-over produces a pericentric inversion.

of a DSB in the Yq copy of IR1 by intrachromatid crossing-over with the Yp copy would lead to a pericentric inversion in that chromatid. Although pseudoisoY chromosomes and Y-chromosome pericentric inversions have been described previously [15–26], it is unknown if these rearrangements indeed are generated via homologous recombination between inverted amplicons.

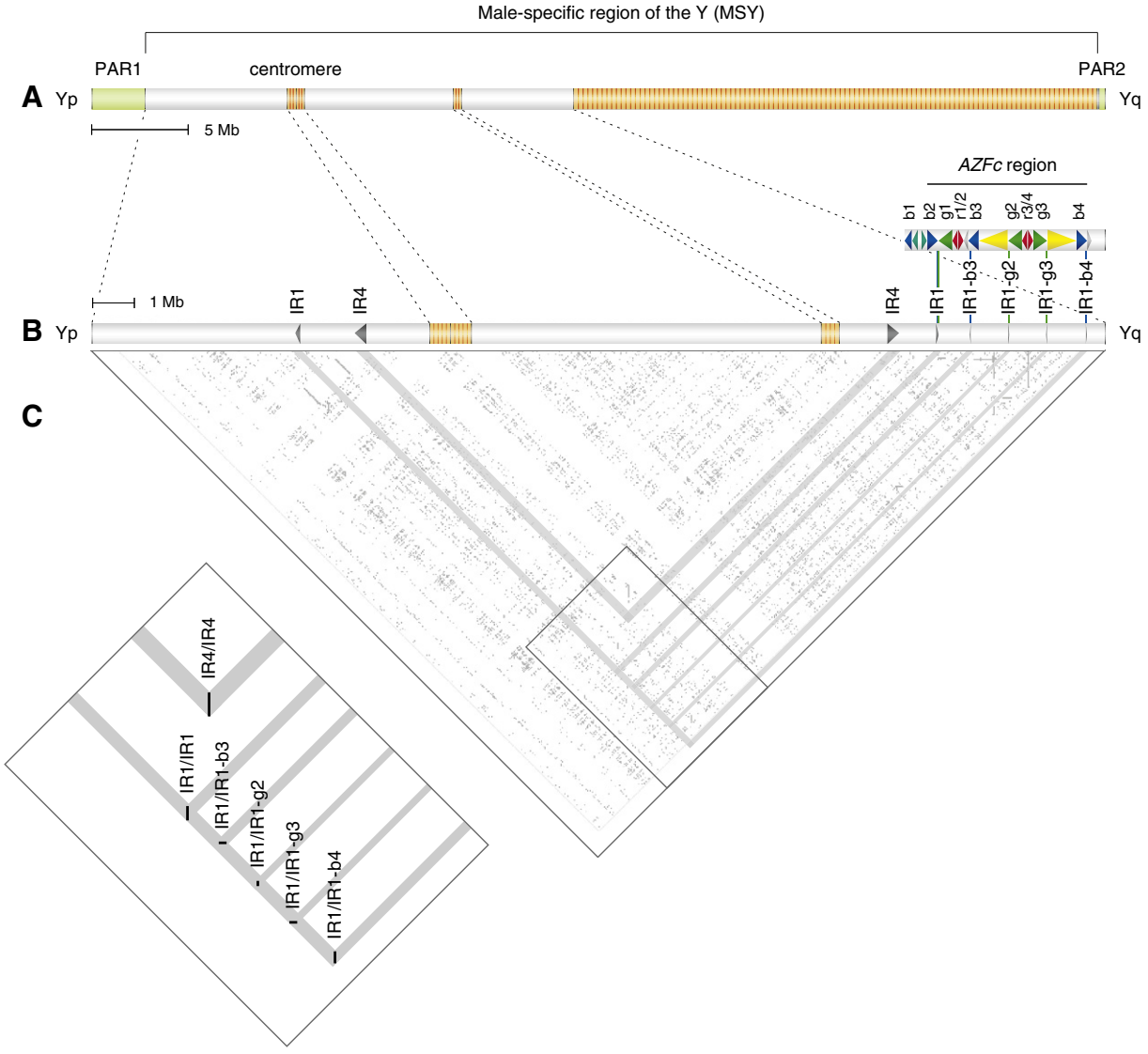


**Fig. 2.** Locations and orientations of Yp–Yq inverted repeats on the human Y chromosome. (A) Schematic representation of the human Y chromosome. The male-specific region of the Y chromosome, or MSY, is flanked by two pseudoautosomal regions, PAR1 and PAR2 (green), and contains blocks of heterochromatin (orange). (B) Inverted repeats IR1 and IR4 are composed of one amplicon on the short arm (Yp) and one amplicon on the long arm (Yq). In addition, segments of IR1 are repeated distally to IR1 on Yq in the highly ampliconic *AZFc* region: IR1-b3, IR1-g2, IR1-g3, and IR1-b4. (C) Triangular dot plot of the reference sequence shows length and orientation of each repeat pair. Each dot represents a 100% match over a window of 100 bp. Repeat elements have been masked. Inverted repeats appear as vertical lines, direct repeats as horizontal lines. Diagonal shading added to highlight the inverted repeats studied here. A magnification of the region bounded by the rectangle is schematized at bottom left.