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REVIEW

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The evolutionary journey of the Y chromosome

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ABSTRACT • Human X and Y chromosomes first formed about 200-300 million years ago in eutherian mammals. Afterwards, sex chromosomes evolved separately in birds, reptiles, amphibians and fish. Classic genetic studies showed that some species have completely lost their Y chromosomes. For example nematodes have XX and X0 chromosomes. The sex chromosomes began their evolutionary journey as an ordinary pair of autosomes. A mutation in the *SOX3* gene (*SRY*-related HMG-box), produced the *SRY* gene, a critical determinant of maleness. However, another gene *RPS4* (ribosomal protein small subunit, protein 4) retained a similar function on both the X and Y chromosomes. Internal recombination events caused a rearrangement of genes on the Y chromosome which meant that large portions of the X and Y chromosome no longer recombined. Deletions on the non-recombinant Y made it decrease in size. However, the donation of a block of genes from an autosome 130 million years ago to both the X and Y, allowed recombination between them. As a result of these changes, Y chromosome is about one-third the size of its partner, the X-chromosome. The knowledge about the evolution of the Y chromosome might shed light on identifying the reasons of infertility.

INTRODUCTION

In male meiosis, the X and Y chromosomes normally pair by segments at the end of their short arms (Xp and Yp) and undergo recombination in that region. The pairing segment includes the pseudoautosomal region of the X and Y chromosomes so called because the X and Y linked copies of this region are essentially identical to one another and undergo homologous recombination in meiosis I, like pairs of autosomes. There is also a second, smaller pseudoautosomal segment which is located at the distal ends of Xq and Yq. By comparison with autosomes and the X chromosome, the Y chromosome is relatively gene poor and contains only about 50 genes. Notably the functions of a high proportion of these genes are related to gonadal and genital development.

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The current view is that, development into an ovary or a testis is determined by the coordinated action of a sequence of genes that leads normally to ovarian development when no Y chromosome is present or to testicular development when a Y is present. The ovarian pathway is followed unless a Y-linked gene, designated testis-determining factor *(TDF)*, acts as a switch, diverting development into the male pathway.

Y CHROMOSOME GENES

a) The testis-determining gene, *SRY*

The earliest cytogenetic studies established the testis-determining function of the Y chromosome. In the ensuing three decades, different deletions of the pseudoautomsal region and of the sex-specific region of the Y chromosome in sex-reversed individuals were used to map the precise location of the primary testis determining region on Yp.

Whereas the X and Y chromosomes normally exchange in meiosis I within the Xp/Yp pseudoautosomal region, in rare instances, genetic recombination occurs outside of the pseudoautosomal region, leading to two rare but highly informative abnormalities: XX males and XY females. XX males are phenotypic males with a 46,XX karyotype who usually possess some Y chromosomal sequences translocated to the short arm of the X. Similarly, a proportion of phenotypic females with a 46,XY karyotype have lost the testis-determining region of the Y chromosome.

The *SRY* gene, which lies near the pseudoautosomal boundary on the Y chromosome, is present in many 46,XX males, and is deleted or mutated in a proportion of female 46,XY patients, thus strongly implicating *SRY* in male sex determination. When a rat *SRY* gene is given to an XX rat, it can induce testis formation all by itself. Thus, by all available genetic and developmental criteria, *SRY* is equivalent to the *TDF* gene on the Y chromosome.

b) Y- linked genes in spermatogenesis

Interstitial deletions in Yq have been associated with at least 10% of cases of nonobstructive azoospermia (no sperm detectable in semen) and with approximately 6% of cases of severe oligospermia (low sperm count) (1). These findings suggest that one or more genes, termed azoospermia factors *(AZF)*, are located on the Y chromosome, and three nonoverlapping regions on Yq *(AZFa, AZFb* and *AZFc)* have been defined. Molecular analysis of these deletions has led to identification of a series of genes that may be important in spermatogenesis. A 10-year retrospective study (2) suggested that *AZFc* deletions are closely related to phenotypic variation in sperm, whereas complete deletions of *AZFb* and *AZFc* are associated with Sertoli-cell-only syndrome (3). For example, the *AZFc* deletion region contains several families of genes expressed in the testis, including the *DAZ* genes encoding RNA-binding proteins expressed only in the premeiotic germ cells of the testis. It was discovered that *DAZ* containing Yq deletions were de novo formations and further research revealed that these infertile men didn't have fertile fathers or brothers with these mutations. Approximately 2% of otherwise healthy males are infertile because of severe defects in sperm production, and it appears likely that de novo deletions or mutations account for at least a proportion of these. Due to the fact that there are at least two more deletion regions proximal to the *DAZ* region on Yq, not all male infertility cases can be linked to *DAZ* deletions

Y LINKED CHROMOSOMAL DISEASES

a) Klinefelter syndrome (47,XXY)

Nearly half of the Klinefelter cases are caused by failure in recombination of normal Xp/Yp in pseudootosomal region which leads to a failure in meisosis

Except 47,XXYY, Klinefelter syndrome has a few cariotypic variants including 48,XXYY, 48,XXXY

and 49,XXXY. As a rule, the additional X chromosome causes a correspondingly more severe phenotype, with a greater degree of dysmorphism, more defective sexual development, and more severe mental impairment.

b) 47,XYY syndrome

The cause of the failure leading XYY karyotype is sticking together in paternal meiosis 2 when forming YY sperm. The likely cause of less seen XYY and sharing Klinefelter-like characteristics XXYY and XXXYY is not seperating in meiosis 1 and 2, consecutively.

c) 46,XX male and 46,XY female

SRY is a DNA binding protein that damages chromosome structure by bending DNA. During normal development, *SRY* is needed for formation of male genitals and its absence causes formation of female genitals. The effecting mechanism of *SRY* on male genital development isn't absolutely known but some remarks make us think *SRY* suppresses a negative regulator of testis development.

In XY females, *SRY* mutations cause *SRY* function loss. 10-15% of XY females have deletion in *SRY*. Also 10-15% has dot mutation in *SRY*. Dot mutations in *SRY* affect DNA binding and bending.

Translocation of *SRY* from Yp to Xp is *SRY* loss in XX males. During male meiosis there is a necessary crossing over between Xp and Yp's pseudootosomal regions, which insures homolog recombination cromosomes' proper segregation and secures the permanence between X and Y'S pseudootosomal regions. But sometimes sentromeric recombination happens in pseudootosomal region and it leads to transferring of some Yp-unique gene sequences including *SRY*. In addition to *SRY*, Y chromosome has at least three more loci for normal sperm devolopment (azoospermis factor *AZFb AZFc*). Absence of those loci explains *SRY* + XX male infertility causes partially (4).

Evolution of Y chromosome

First step in evolution of Y chromosome is the acuisition of male-specific gene gain, in which recombination between homomorphic proto-sex chromosomes should be suppressed. This suppression secures the evolution of Y chromosome being apart from X (5,6). The result of these though, non-recombining Y chromosome shows low level of adaptation activity. In other words, increase of high amount of harmful mutation and low adaptation skill are proportional with excess of recombination areas in different species (7,8).

Another specialty of Y chromosome is being transferred from father to son, so Y chromosome can be never transferred by a female individual. Male-limited transfer signifies that Y chromosome carries necessary parts for mankind in genome, since male-specific characteristics are transferred while protecting Y chromosome from antagonistic sexual evolution and counter selection (8-10). That's why estimations about gene content of Y chromosomes are clear, gene deletions are more seen and Y-related genes are rich from male beneficial functions (7,8).

Evolutionary ancestors of sex chromosomes are a pair of autosomal chromosome which includes sex determining genes on one of the matching pairs. This appeared on a reptile-like ancestor 350 million years ago. In time male specific genes appeared on proto-Y and because of this, proto-Y lost its ability of recombination with proto-X. There are 4 different gene areas that have taken part on the loss of recombination between of proto-X and proto-Y over 4 different steps of time. Each of these 4 areas has increased the amount of mutation in the non-recombinant parts of proto-Y. In time proto-Y evolved into the Y chromosome and because of the degradation in the non-recombinant parts of the chromosome, it lost most of its genetic information. Its pair evolved into the X chromosome. The degradation of the Y chromosome is triggered by addition of autosomal genes in different times (like in

the X chromosome) and it caused a pattern of loss and gain of genetic material throughout time (11).

ORIGINALITY OF THE Y CHROMOSOME

Why do we focus on the part of the genome that gives us information about only the half our population? Because of its gender defying role, the Y chromosome is naturally haploid and specific for male. It passes from father to son and unlike other chromosomes Y chromosome escapes largely from meiotic recombination. The parts with two segments (pseudoautosomal regions) can recombinate with X but these parts are only the 3 Mb long parts of 60 Mb long Y chromosome. The importance of escaping recombination is that the marker alleles can be passed on to generation to generation without changing. They don't change with complicated processes like "reshuffling" and they can only be changed by mutations. Therefore it is expected that the Y chromosome has a lower rate of variation compared to other chromosomes and that it is more open to the possibility of random changes in the haplotic frequency. This random change accelerates diversity between different populations.

Because of the fact that the Y chromosome is only transferred by male germ line cells, it is more affected by mutagenic properties. The Y chromosome is rich with repetitive sequences that have low copies and non-allelic homologue recombination between these paralogues can cause non-pathogenic rearrangement and infertility for men via *AZFa, AZFb* and *AZFc* deletions. In both of these situations, there are evidences of gene exchange between paralogues. It is expected that by comparison to the base substitutions, such events would occur more often and it may affect the odds of rearrangement of the sequence identity's length. The Y specific microsatellites are not detectibly different from their autosomal equivalents and this is a sign that the mutations in these markers are contained substantially or completely in the allele and this mechanism is compatible with replication slippage mechanism. For the reason that the non-recombinant part of the Y chromosome do not contain highly variable G-C microsatellites, it is believed that these parts are the by-products of recombination.

As a result, the typical features of the Y chromosome come together to create a fast evolutionary change.

CONCLUSION

The future of the Y chromosome and whether if the gene losses on the chromosome are still continuing are subjects for scientific researches for a long time. These researches showed that the degeneration of the Y chromosome is not continuing linearly and the shortenings are protected on some level (12,13). The finding about the Y chromosome of *Rhesus macaque,* which got separated from men 30 million year ago in the evolutionary step, having the same length as men consolidates this opinion (14). It is thought that in the future the level of deletion will stand still.

The studies of the Y chromosome give us information for which evolutionary steps the Y chromosome has completed and what is expected to happen in the future. The expanding knowledge on Y chromosome evolution is important for creating new ways to look at Y chromosome related hereditary diseases and for identifying possible reasons of infertility.

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