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THE STRUCTURE OF THE Y CHROMOSOME - A COMPARATIVE MINIREVIEW OF DIFFERENT ORGANISMS

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Abstract: Y-chromosome is composed of large regions of non-recombinant sequences and transmitted only through the male sex. In 1959, when Patricia Jacob studied Klinefelter syndrome (XXY) and Charles Ford studied Turner syndrome (X0) concluded that Y-chromosome is determined by sexes. Y-chromosome originates from autosomes and its evolution has often been associated with large deletions and inversions. Recent studies of sex chromosomes in humans and other primates, as well as in plants and Drosophila, throw light on its structure and origin. Classical genetic studies have shown that the Y-chromosome contains an extremely small number of genes, some even disappeared in some species.

After sequencing the human genome, it is possible to study the molecular structure of the Y-chromosome. About 95 % of its length is not participating in recombination with X-chromosomes and is called NRY (nonrecombining region). The other part of the Y-chromosome is called MSY (male-specific region. Euchromatin sequences in MSY are separated into three regions: the X-transposed region, the X-degenerative region and the ampliconic region.

Recent studies suggested that the X and Y chromosomes are diverge 300 million years ago. Comparative analysis of Y chromosomes at different stages of differentiation in different organisms will give additional information on the structure and evolution of the sex chromosomes.

The organization of the human Y chromosome

Human sex chromosomes (X and Y) are thought to have evolved from a pair of autosomes when an ancestral mammalian developed an allelic variation called the "sex locus." This locus determined which chromosome to be Y-chromosome and the male sex. Genes that have been useful to males and harmful or not effective to females are transferred to the Y chromosome through translocation.

After sequencing the human genome, it became possible to study the molecular structure and function of the Y chromosome. Genomic studies have provided evidence of intrachromosomal recombination leading to the formation of the male-specific region (MSY) (fig.1).

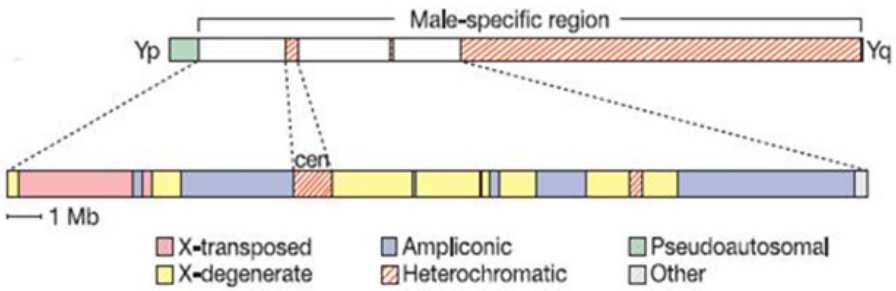

Figure 1. Male-Specific Region of the Y chromosome (Skaletsky et al., 2003).

The male-specific region (MSY) of the Y chromosome is the only haploid part of the nuclear genome. It covers about 95% of the whole chromosome and is contained three different classes of euchromatic regions: X-transposed, ampliconic and X-degenerate (Skaletsky et al., 2003). The X-transposed region is 99% identical to the long arm of the X chromosome (Ross et al., 2005). X-degenerate sequences are parts of ancient autosomes and the amplicon region is characterized by a large number of intrachromosomal duplications and contains genes that are expressed primarily in the testes (Skaletsky et al.,2003; Rozen et al., 2003). There are 8 massive palindromes in the ampliconic region termed P1–P8. There are two highly similar intra-chromosomal inverted palindrome arms separated by a non-duplicated spacer (Rozen et al., 2003; Hallast et al., 2013).

Identical palindrome regions are preserved or independently formed and belong to different kingdoms (Ezawa et al., 2006; Davis et al., 2010; Méndez-Lag et al., 2011; Tomaszkiewicz et al., 2016; Trombetta et al., 2017; Swanepoel, 2020; Zhou et al., 2020). Large palindromes are overrepresented in the mammalian X chromosome (Warburton et al., 2004; Mueller et al., 2008; Mueller et al., 2013) and, like Y palindromes, may undergo gene conversion events (Swanepoel et al., 2020). David Page's group has published the first complete sequence of a 23 megabase (Mb) euchromatic region, including 8 Mb on the short arm (Yp) and

14.5 Mb on the long arm (Yq) of a human Y chromosome (Skaletsky et al., 2003). The data showed a detailed picture of the organization of a Y chromosome. The MSY region contains at least 158 transcription units, half of which probably encode proteins. They are a small part of 160 Mb on the X chromosome (International Human Genome Sequencing Consortium: Initial sequencing and analysis of the human genome. Nature. 2001, 409: 860-921). The coding sequences among these 158 units can be divided into two categories. The first category includes 27 genes that are homologous of the genes on the X chromosome. 14 of them are actively linked to the Y chromosome and are expressed in many different tissues. The exception is the male defining gene, Sry, which is expressed in germ cells and has an X analog, Sox3 (Lahn et al., 1999). The second category consists of 9 gene families which are different from the X chromosome genes. They are organized in two or more repeats. Interestingly, two of them come from the X chromosome, and the other seven were obtained by transposition from autosomes. Similarity transposition from autosome to the Y chromosome was found in the plant *Silene latifolia* (Matsunaga et al., 2003).

Three classes of sequences in the MSY region

The MSY euchromatin region is subsequently sub-divided into three sequence classes:

1) The X-transposed sequences - they are 99% identical to sequences in Xq21. It is believed that about 3-4 MY ago there was a massive transposition from X to Y, which resulted in these sequences (Mumm et al., 1997; Schwartz, A. et al.1998). This was followed by an inversion in the short arm and the modern MSY was obtained (Page et al., 1984). These X-transposed sequences do not participate in X-Y crossover, which makes them different from pseudo-autosomal sequences (in the telomeric regions of human X and Y). X-transposed segments have a combined length of 3.4 Mb. Two genes that have homologs in Xq21 (Skaletsky et al., 2003) have been identified. Considering gene and repeat density, X-transposed sequences show the lowest gene density among the three classes of sequences in MSY euchromatin, but the higher repeat density (Human Genome Sequencing Consortium Initial sequencing and analysis of the human genome, 2001, Nature 409, 860–921; Venter, et al. 2001).
2) X-degenerative region - the X-degenerate segments of MSY have a single copy of 27 X-linked genes and show between 60% - 96% nucleotide sequence similarity with their X-linked homologs. They are ancient relics of autosomes from which the sex chromosomes evolved. 13 of them are pseudogenes, while in the remaining 14 cases the MSY homolog is a transcribed functional gene (Skaletsky et al., 2003). All 12 expressed MSY genes are located in the X-degenerated regions. 11 MSY genes were found to be expressed in the testes, only one SRY sex-determining gene was X-degenerated.

3) Ampliconic region - They are composed mainly of sequences that show up to 99.9% similarity to over tens or hundreds of kilobases in MSY. These long, repetitive units, of which there are many families, are called amplicons. They are located in seven segments, which are along the length of the long arm and the proximal short arm, and the total length is 10.2 Mb (Skaletsky et al., 2003). It should be noted that 60% of the ampliconic sequences show 99.9% or more intrachromosomal identity. Amplicon sequences contain coding and non-coding genes. There are nine different MSY protein-coding gene families, and the number of copies can range from two (eg. HSFY, VCY, XKRY, PRY), three (BPY2), four (CDY, DAZ) to 35 (TSPY). Copies may vary for different Y chromosomes in human populations. All these nine families comprise about 60 transcription units. There are also 75 additional transcription units, which are members of 15 MSY-specific families.

Palindromes on the Y-chromosome

Y chromosome repeats are organized as palindrome structures. There are eight massive palindromes, which arms are symmetrical and nucleotide similarity of 99.94-99.99%. Palindromes are long, each contains a unique and non-duplicated spacer at its center. P1 is large (2.9 Mb) and carries two secondary palindromes (P1.1 and P1.2) (Kuroda-Kawaguchi, et al. 2001). The 8 palindromes together are 5.7 Mb or one-quarter of the MSY euchromatin region. Some of these palindromes are present in chimpanzees, so their origin precedes the separation between people and their close relatives (Rozen et al., 2003) (fig.2).

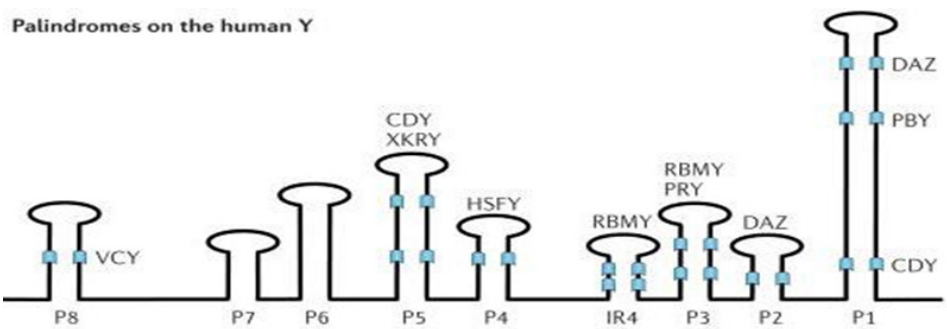

Figure 2 Palindromes on the human Y chromosome (Bachtrog et al., 2013).

Six of the palindromes carry genes encoding proteins that are expressed in the testes. From all nine families coding proteins in MSY, 8 have members in palindromes. They include the DAZ genes and the CDY genes in a different number of copies.

The ampliconic regions of Yq and Yp contain also five sets of spaced inverted repeats. Three of these repeats are pairs (IR1, IR2, and IR3) and show nucleotide identities of about 99.95% (Tilford et al., 2001).

The ampliconic areas also contain long tandem clusters with a no-long open reading frame (NORF) and testis-specific protein, Y-encoded clusters (TSPY) (Vogel et al.,1998; Skaletsky et al., 2003).

X-degenerate and ampliconic regions evolved partly in parallel as parts of a DNA molecule. Both of them were transmitted only through the male germline. They have several differences which suggest different evolutionary events.

Y–Y gene conversion

Recombination between the X and Y chromosomes has proved to be less useful because some of the necessary genes that were previously on the X chromosome are lost for males, while genes that have been on the Y-chromosome for females are harmful. This leads to gene accumulation in males predominantly close to the sex-determining genes, and recombination is suppressed (Graves et al., 2006). So, the Y chromosome changes and the areas around the sex-related genes cannot recombine with the X chromosome. As a result of this "protective" mechanism, 95% of the human Y chromosome is unable to recombine.

In 2003, scientists at the Massachusetts Institute of Technology found a process that can retard the degradation of the Y chromosome. The Y chromosome could "recombine" with itself using palindromic sequences (Rozen et al., 2003). This recombination is called gene conversion and is a type of recombination which involves the non-reciprocal transfer of genetic information from a “donor” sequence to a similar “acceptor” sequence (Chen et al., 2007). Gene conversion does not take place only in genes but may occur in any duplicated area of the genome (Trombetta et l., 2017).

Two modes of recombination in the human Y chromosome occur regularly. First, there is a crossing-over with the X chromosome in the PAR (pseudoautosomal) regions, and second, there is Y–Y gene conversion (Rozen et al., 2003). These models of Y chromosome recombination are called ‘productive’ to differentiate them from the rare or aberrant recombinations which disturb sex differentiation or fertility.

Scientific data show that multiple Y-Y gene conversion events occur per generation in MSY while X-Y crossing-over occurs in pseudoautosomal regions in one generation of MSY.

Human Y-chromosome - comparisons with other species

Sex chromosomes are derived from autosomes and have evolved in different lineages. They carry the genes determining sex and are subject to evolutionary forces (Charlesworth et al., 2000; Bachtrog et al. 2011). Some Y chromosomes like those of humans and Drosophila, and some species of plants are subjected to a process called degeneration. In this process, the Y chromosome loses most of the original genes and acquires new ones that are useful for males (Bull JJ., 1983; Charlesworth B, and Charlesworth D., 2000).

Old Y-chromosomes of Drosophila melanogaster and human, are highly heterochromatic with a large number of repeats and ampliconic DNA (The Chimpanzee Sequencing and Analysis Consortium Initial sequence of the chimpanzee genome and comparison with the human genome, 2005, Nature, 437:69–87). The X and Y chromosomes of humans and other mammals evolved from a common ancestral chromosome over 200 MY ago. All members of Drosophila have a homologous ancestral sex chromosome pair that formed over 60 MY ago. These data show that the Y chromosomes of these species diverge in the evolution. The research analysis of D. melanogaster Y chromosome and primate Y chromosomes revealed common characteristics shared between their Y chromosomes.

Y chromosomes of the three species of primate, human, rhesus macaque, and chimpanzee are sequenced (Skaletsky et al. 2003; Hughes et al. 2005; Hughes et al., 2010; Hughes et al. 2012).

They differ in gene content and sequence. The chimpanzee MSY area contains twice more massive palindromes as the human MSY and has lost much of its genes and part of the gene families. In both chimpanzees and humans, the ampliconic and X-degenerate sequences are the most of the MSY euchromatin region (Hughes et al., 2010). These sequences in the human MSY are the result of an X-Y transposition that occurred after the divergence of humans from the chimpanzee lineage (Page et al., 1984). Comparing the human and chimpanzee MSY, it was found that there is a large sequence loss of the ampliconic regions. The chimpanzee ampliconic areas are massive and contain 19 palindromes. Seven of them are found in human MSY, and the other 12 are specific to chimpanzees. Unlike human MSY, almost all chimpanzee palindromes are in multiple copies (Hughes et al., 2010). While humans and chimpanzees contain a substantial amount of amplicon DNA, it is almost absent in rhesus as well as the euchromatic segment of the MSY is notably smaller in rhesus. (Hughes et al., 2012). The Human X-degenerate region contains 16 single-copy genes with X-homologs (Skaletsky et al., 2003). All of these 16 genes are shared between humans and rhesus. The chimpanzee X-degenerate regions had lost 4 of 16 genes due to mutations (Hughes et al., 2005).

The Y chromosome of D. melanogaster also has its characteristics and is crucial for male fertility. About 40 Mb is heterochromatic and a small part of it

contains protein-coding genes (Kennison JA, 1981; Carvalho et al. 2003).

Male drosophila without Y is viable but sterile (Brosseau, 1960). Studies of the Drosophila Y chromosome identified six fertility factors of Drosophila (Gatti and Pimpinelli, 1983). Some of them are more than 100 times larger than a single Drosophila gene (Bonaccorsi et al., 1988). Comparing the Y chromosome gene content in the 12-sequenced Drosophila species revealed that only three of the Y-linked genes of D. melanogaster are in all species (Koerich et al., 1990; Williams et al., 1990). There is only one homologous region between the X and Y chromosomes in D. melanogaster, the rDNA locus. It is a tandem repeating array consisting of hundreds of units encoding ribosomal RNA genes (McKee and Karpen, 1990).

In humans, the euchromatic region of the Y contains 78 protein-encoding genes, while the heterochromatic Y chromosome in Drosophila contains only 13 protein-encoding genes. Genomic sequencing also confirms that many male function genes are located on the Y in both primates (Lahn and Page, 1997) and Drosophila (Gatti and Pimpinelli, 1983; Carvalho et al., 2001). In addition, the Drosophila Y chromosome did not contain large ampliconic regions, which are present in the human Y chromosome (Skaletsky et al., 2003).

Unlike animals, most terrestrial plants are cosexual (female and male reproductive functions in one individual). Only about 6% of the plant have developed separate sex, which sometimes leads to appearance of heteromorphic sex chromosomes. A recent analysis of *Silene latifolia,* provided initial evidence for the structure of the sex chromosomes of plants (Westergaard, 1958; Lardon et al, 1999; Ming et al., 2011). The two sex chromosomes of *S. latifolia* contain approximately 4000 genes and are morphologically different (Bernasconi et al.2009)(Fig.3).

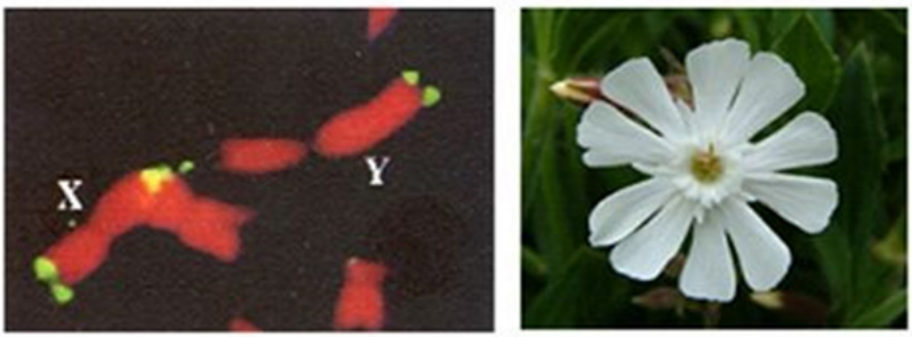

Figure 3. Sex chromosomes of *S.latifolia* (Lardon et al., 1999).

Transcriptome analysis identified about 400 gene pairs of X and Y, and gene expression levels were significantly lower in Y-linked genes compared to their X homologs. The data show that Y usually degenerates much more slowly in plants than in animals (Chibalina et al., 2011; Bergero and Charlesworth, 2011). The explanation for these differences is due to the expression in haploid gametes in plants carrying the Y chromosome. In them, pollen expresses many genes, while in animals sperm show much more limited gene expression (Schafer et al., 1995). The first Y-linked genomic sequence for plants was published after research on papaya (Wang et al. 2012). The study showed two different Y chromosomes that control the males and hermaphrodites development. When comparing the two Y chromosomes, it was found that the hermaphrodite Y sequence has two large inversions. The increase in the size of the Y-chromosome was found due to the insertion of a retrotransposon into Y (Wang et al. 2012). While the loss of genes from plant Y chromosomes can be delayed compared to animals, non-recombinant chromosomal degeneration, which is an even more common phenomenon cannot be delayed.

CONCLUSIONS

Y-chromosome originates from autosomes and its evolution has often been associated with large deletions and inversions. Genes, which were beneficial for males and harmful to females, are saved on the Y chromosome. Through the process of translocation, other genes are transferred to the X chromosome. Recent studies of the Y- Y-chromosome in humans and different primates, as well as in plants and Drosophila, throw light on its structure and origin.

After sequencing the human genome, it became possible to study the molecular structure of the Y-chromosome. About 95 % of its length is not participating in recombination with X-chromosomes and is called NRY (nonrecobinating region). The other part of the Y-chromosome is called MSY (male-specific region) and is predominantly responsible for male sex determination.

The structure of Y chromosomes continues to be a challenge, but new sequencing technologies will help study their sequences.

Questions arise that still need to be answered. Are amplicons unique to all primates? Are the characteristics found in model organisms general to all Y chromosomes? Are the large introns in Drosophila Y chromosome characteristic for Y-chromosomes of other organisms? And why do birds have two homologous sex chromosomes? All these questions, and many more, are looking for answers.

Many scientists predict the future evolution of the Y chromosome. They suggest that the Y chromosome will disappear and other chromosomes will take over its genes and functions as in some species (Sutou et al., 2001; Zhou et al., 2008; Matveevsky et al., 2017).

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