Review article:

"Y chromosome: Structure and Biological Functions"

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Abstract:

Y chromosome is the smallest haploid sex chromosome. Although Y chromosome is poor in genes, it comprises several important genes which plays essential role in different biological functions- Sex determination, regulation of spermatogenesis as well as in male infertility. This paper details about the structure and various important functions of Y chromosome.

Keywords : Y chromosome , Sex chromosome

Introduction

Y chromosome is the sex chromosome and is one of the smallest chromosomes in the human genome (~ 50 million bp) which represents around 2%–3% of a haploid genome. Human Y chromosome is known as "gene poor chromosome" but it plays a fundamental role in human biology as its presence or absence determines gonadal sex. Besides this, Y chromosome also plays an important role in the regulation of spermatogenesis and hence in male infertility. It has occupied exclusive position in the human genome owing to its size, organization and function. This paper details the structure and the biological functions of this peculiar chromosome.

Cytogenetic structure

Y chromosome is acrocentric, and therefore it has a short p arm (designated Yp) and long q arm (designated Yq), clearly separated by a centromeric region, essential for chromosomal segregation in the male meiosis. Euchromatin region constitutes the short arm Yp, centromere and proximal long arm, while the heterochromatin region is the distal long arm (Yp),[1] combined are referred to as MSY (male specific region), approximately 95% of the Y chromosome while remaining 5% of the chromosome are Pseudoautosomal regions (PAR) [2].

Cytogenetic partition of y chromosome includes the euchromatic short arm. This is designated as Yp11 whereas long arm Yq is divided into a euchromatic proximal region Yq11 and heterochromatic distal region Yq12. The Yq11 band is further subdivided into sub-bands Yq11.1, 11.21, 11.22, and 11.23 respectively (fig1) [3].

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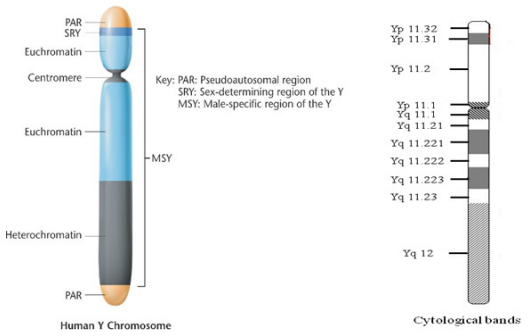

Fig1: Human Y chromosome [4]

Fig2: Cytological bands on Y Chromosome[5]

Pseudoautosomal regions (PARs) : Pseudoautosomal regions (PAR) are homologous sequences of nucleotides which are located on either end of the chromosome (at the telomeric tips). PAR1 is at the distal part of the short arm (Yp), and is approximately 2.5 Mb in length. At the distal part of the long arm (Yq) is PAR2, which is less than 1 Mb in length [2]. Both harbour the homologous genes that recombine with the homologous genes of the X-chromosome during male meiosis [6]. To date 24 genes have been discovered for PAR1 while only 4 genes have been discovered for PAR2 [7]. One of the important gene that resides on the PAR1 is *SHOX* (Short stature HomeoboX-containing) gene which is known to be involved in the short stature in Turner syndrome [8].Another gene is MIC2 (major immunogene complex) that encodes for an integral membrane glycoprotein CD99. This is located on the short arm at Yp11.3 that undergoes crossing over with an allele on the short arm of the X-chromosome at Xp22.23 [2].

Male Specific Region of Y chromosome (MSY) The event of recombination is limited to the extremities that are pseudoautosomal regions (PAR) which accounts for only 5% of the total chromosome [3]. The region excluding the PARs does not involve in meiotic recombination and is called Male Specific region of Y chromosome (MSY), which accounts for 95% of the Y chromosome length [2].The male specific region of Y chromosome contains both euchromatic and heterochromatic sequences. The heterochromatic region is assumed to be genetically inert and polymorphic in length in different male populations, because it is composed mainly of two highly repetitive sequence families, DYZ1 and DYZ2. These sequences contain about 5000 and 2000 copies of each alphoid repeat sequences, which are clustered tandemly near to the Y-chromosome centromere that includes the major SINE (Short interspersed elements), Alu repeat sequences important for spermatogenesis [9].The euchromatic MSY is divided into three classes of sequences - **X transposed** which is two sequence blocks present on Yp (short arm), **X degenerate** is eight sequence blocks on both short arm Yp and the long arm Yq and **ampliconic sequences** which is seven large sequence blocks on both the short arm Yp and the long arm Yq [2] .The X transposed sequences are the ones that have been acquired by the process of transposition from the X chromosome about 3-4 million years ago [10]and hence it has 99% identity with the long arm of the X chromosome. X-degenerates are the single-copy genes or pseudogene homologues of X-linked genes. This region harbors 27 different X-linked single copy genes, 13 of which are non-functional pseudogenes that contain similar sequences to that of the introns and exons of the X homologue [2].Ampliconic sequences are characterized by sequence pairs showing nearly complete (>99.9%) identity, organized in massive palindromes. Ampliconic sequences comprise 60 coding genes and 74 non-coding transcription units that express primarily in

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the testis. Ampliconic sequences recombine through non-reciprocal transfer of sequence information occurring between duplicated sequences within the chromosome. This process of gene conversation maintains the >99.9% identity between repeated sequences organized in pairs in inverted orientation within palindromes. Also this peculiar sequence organization provides the structural basis for deletions and rearrangements through the homologous recombinations [11].

Genes on Y chromosome:

Uptil now,156 transcription units together with 78 protein-coding genes encoding 27 proteins have been report in the MSY2.These genes are divided into two categories based on their site of expression - expressed ubiquitously and expressed specifically in the testes (table 1). The examples of the genes known for ubiquitous expression are USP9Y, DBY and UTY. These genes have X homologs and are present in single copy on Y chromosome. On other hand genes that are expressed mainly in testis are RBMY1, DAZ, CDY etc. which are present in multiple copies and are predominantly involved in the male gametogenesis [12, 3].

Table 1: Genes on Y chromosome (All the information about the genes is annoted in genetic reference home,Genebank)

Gene symbol	Protein encoded	Transcription pattern	Associated function / Pathology	X homologs
USP9Y	Ubiquitin-specific protease 9 Y	Ubiquitous	Azoospermia	USP9X
DBY	Dead box Y	Ubiquitous	Complete or severe reduction in male germ cells	DBX
UTY	Ubiquitous TPR motif Y	Ubiquitous	Spermatogenetic impairment	UTX
AMELY	Amelogenin Y	Teeth	Tooth formation?	AMELX
TBL1Y	Transducin (beta)-like 1 protein Y	Fetal brain, prostate	Lissencephaly	TBL1X
ZFY	Zinc finger Y	Ubiquitous	Turner syndrome	ZFX
PCDH11Y	Protocadherin 11 Y	Fetal brain, brain	Multiple congenital abnormalities	PCDH11X
NLGN4Y	Neuroligin 4 isoform Y	Fetal brain, brain, prostate, testis	Asperger syndrome	NLGN4X
TMB4Y	Thymosin (beta)-4 Y	Ubiquitous	Infertility	TMSB4X
EIF1AY	Translation initiation factor 1A Y	Ubiquitous	Infertility	EIF1AX
TGIF2LY	TGF (beta)-induced transcription factor 2-like Y	Testis	Azoospermia	TGIF2LX

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TSPY	Testis-specific protein Y	Testis	Gonadoblastoma	-
RBMY	RNA-binding motif Y	Testis	Sertoli cell only syndrome	RBMX
PRY	PTP-BL related Y	Testis	Sperm apoptosis	-
DAZ	Deleted in azoospermia	Testis	Oligospermia,azoospermia	DAZL
BPY2	Basic protein Y	Testis	Infertility	-
CDY	Chromodomain Y	Testis	spermatogenetic failure,azoospermis	CDYL
HSFY	Heat shock transcription factor Y	Testis	Azoospermia	-
XKRY	XK related Y	Testis	Spermatogenetic failure	-
SRY	Sex determining region Y	Predominantly testis	Sex reversal	SOX3
VCY	Variable charge Y	Testis	Infertility	VCX

Functional roles of Y chromosome

Several important genes contributing to maleness as well as sex determination are expressed on y chromosome. Hence the important roles of this chromosome are sex determination, male germ cell development and its maintenance.

Sex Determination

In mammals sex determination is genetically determined. This was proved for the first time in 1959 when two human Disorders of Sex Differentiation (DSDs), Turner syndrome (XO females) and Klinefelter syndrome (XXY males) were identified and reported[13, 14]. These studies established that the Y chromosome carries a gene that determines maleness. The discovery of SRY (sex-determining region on the chromosome Y) took almost thirty years. The human SRY gene was identified by searching for conserved sequences among translocated Y chromosomal DNA from four XX male patients [15]. The role of SRY as the switch gene for mammalian sex determination was confirmed in experiments in which XX mice were converted to males by the introduction of SRY [16]. SRY protein is a transcription factor of high mobility group (HMG) family [15] .In mammals sry expression initiates the sex specific gonadal development in somatic gonadal cells. SRY gene then up regulates the activity of several genes which are concerned to the sertoli cell differentiation. Differentiating Sertoli cells then organize into testis cords which then stimulate the male specific development of germ cells that will form testis [17].

Genetic regulation of spermatogenesis-

The role of Y chromosome in speramatogenesis was studied for the first time by Tiepolo and Zuffardi after screening six azoospermic patients for cytogenetically detectable *de novo* deletions [18]. These observations led the authors to postulate the existence of a locus, called Azoospermia Factor (AZF), on Yq11 required for occurrence of complete spermatogenesis since the seminal fluid of these patients did not contain mature spermatozoa. This was further confirmed by numerous studies at both the cytogenetic and molecular levels [19,20,21]. In 1996, Vogt and co-workers screened 370 men with idiopathic azoospermia or oligozoospermia for deletions, using 76 sequence tag siteswrite full form (STSs). Their findings suggested the existence of

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three non-overlapping regions within the *AZF* locus; designated from proximal to distal, as "*AZF*a", "*AZF*b", and "*AZF*c", respectively. Each one of these regions contains several genes proposed as candidate genes involved in male infertility [22].

The AZFa region is located in proximal Yq within the deletion interval 5 where it spans roughly between 1 and 3 Mb. Different genes have been identified in this region, like ubiquitin-specific protease 9 Y chromosome gene (*USP9Y*), DEAD box Y gene (*DBY*), ubiquitously transcribed tetratricopeptide repeat Y chromosome gene (*UTY*). DBY, the main gene of AZFa region is expressed in the testis and is involved in the development of pre-meiotic germ cells suggesting its role in infertility [23]. The USP9Y gene is also involved in spermatogenesis [24]. Shortening or deletion of the USP9Y gene causes azoospermia, oligozoospermia [25] or oligoasthenozoospermia. Deletions in the AZFa region that remove both of these genes cause Sertoli cell–only syndrome, a condition characterized by the presence of complete Sertoli cells in the testes but a lack of spermatozoa in the ejaculate [23].

The AZFb region is located between deletion interval 5 and proximal deletion interval 6, and it spans similar to that of the AZFa region (1–3 Mb). The genes that have been mapped to the *AZF*b region include *RBMY1*, *PRY, RPS4Y2, HSFY, CDY2, TTY2, TTY5, TTY6, TTY9, TTY10, TTY12, TTY13, TTY14, TTY16, XKRY* genes [23.] Testes specific Transcript Y (*TTY* genes) are described as non-coding genes because they do not have an open reading frame [12,2]; while the role in spermatogenesis for most of the other genes is still to be elucidated. RBMY1 codes for an RNA binding protein [26], which is a testis-specific splicing factor expressed in the nuclei of spermatogonia, spermatocytes, and round spermatids. Lavery *et al* demonstrated that RBMY1 expression was reduced in azoospermic men [27]. Regulation of apoptosis, an essential process that removes abnormal sperm from the population of spermatozoa is done by the PRY (PTP-BL related on the Y chromosome) gene [23]. Deletion in both PRY and RBMY1 results in complete arrest of spermatogenesis [28].

The AZFc region is located in the proximity of the heterochromatin region distal to Yq11 and it spans about 500 kb [29]. Candidate genes within the *AZFc* region include 4 copies of the *DAZ*, 3 copies of *BPY2* (Basic Protein on Y chromosome 2), and two copies of *CDY1* (*CDY1a* and *CDY1b*; Chromodomain protein, Y chromosome 1) [29].

DAZ genes play a variety of roles throughout the spermatogenesis process because they are expressed in all stages of germ cell development [30].They control translation, code for germ cell–specific RNA binding proteins and are involved in the control of meiosis and maintenance of the primordial germ cell population [30].Deletions of the DAZ genes can cause a spectrum of phenotypes ranging from oligospermia to azoospermia [29].

Role in the Brain Function

In humans, sex differences are distinct in terms of brain development, brain function and behavior. Eventually, such differences emerge from the differential sex chromosome present in the males and females: males inherit a single X chromosome and a Y chromosome, while females inherit two X chromosomes. For this, the expression of the male limited genes on Y chromosome could be one of the possible underlying mechanisms demonstrated by Kopsida et al [31]. Many Y-linked genes play an important role in the development of the testes, and hence indirectly contribute to sexual differentiation

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of the brain by influencing gonadal hormone production. Also, Y-linked genes that are expressed in the brain could directly impact on the neural masculinisation [31].

SRY may influence brain and behavior either indirectly, *via* effects on testis development and subsequent hormone secretion, or directly *via* its expression in neural tissue. Case studies or small-scale studies have suggested a role for Y chromosome genes in some neuropsychiatric disorders. For example, individuals with 47, XYY syndrome may be at elevated risk of developing antisocial behavior [32] and schizoaffective disorder [33], possibly as a result of Y linked gene over-expression. A chromosomal aberration, isodicentric Y chromosome in a schizophrenic patient suggests the possible role for Y-linked genes in the pathogenesis of schizophrenia [34]. A case study reported a boy with ADHD with a rare deletion of Yq with duplication of Yp, suggesting the role of the Y-linked genes in ADHD susceptibility [35].Interestingly, the duplicated region included the *SRY* gene, suggesting that over dosage of this specific gene may be responsible (either directly or indirectly) for the observed behavioral phenotype [31].

Role in the development of cancer

The Y chromosome is critical for male development and physiology, such as spermatogenesis. However, dysfunctions of its genes could contribute to diseases such as testicular germ cell tumors, gonadoblastoma.

Testicular germ cell tumour (TGCT) is the most common malignancy in men aged 15–45 years. Recent advances have shown the association of genetic factors on the Y chromosome with the development of TGCTs. Deletion of *gr/gr* region on the human Y chromosome is one of the reasons to be associated with increased risk of TGCTs. It has been reported that this deletion results in a 1.5 fold increased risk in men without a family history of TGCT and a 2.3 fold increased risk in men with a family history of TGCT, and is present in 1% of unaffected individuals [36]. As discussed above, the AZF region also has an important role in male factor infertility .The strong association between reduced fertility and TGCTs could suggest that they share common genetic determinants [37]. Another study done by Linger *et al*, shows deletions of sY1291(STS marker) indicative of 'gr/gr' (8 out of 271; 2.9%), Y-DAZ3 within 'gr/gr' (21 out of 271; 7.7%) and a single deletion of the marker G66152 in one TGCT case [35].

The gonadoblastoma (GBY) locus is the known oncogenic locus on the human Y chromosome. Clues of the oncogenic role of the Y chromosome have come from observations that XY sex-reversed and/or intersex patients develop gonadoblastoma at extremely high frequency in their dysgenetic gonads at early ages [38]. Numerous studies suggest that the testis-specific protein Y-encoded (TSPY) gene is the putative gene for GBY [39, 40]. Indeed TSPY is abundantly expressed in gonadoblastoma and is associated with the oncogenesis of this type of tumors in XY females as well as testicular germ cell tumors (TGCTs), seminomas, selected non-seminomas, intracranial germ cell tumors of male origin, and somatic cancers including prostate cancer, hepatocellular carcinoma and melanoma. According to Lau *et al*, abnormal TSPY expression initiates the protein synthesis, accelerates cell proliferation, and encourages tumorigenicity in athymic mice [41]. TSPY binds to type B cyclins, accelerates an activated

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cyclin B-CDK1 kinase activity, and accelerates the transition of G2 to M phase in the cell cycle.

On the concluding notes, Y chromosome is exceptional in various aspects.It is in haploid state and comprise of many repeated sequences. Though it is the smallest chromosome, it plays important biological roles - SRY gene plays important role in sex determination and male gametogenesis as well as in the brain function.Genes located on the AZF region of Y chromosome are important for male fertility.Thus Y chromosome is an important component of the human genome.

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