The Human Y Chromosome

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Learning Objectives

- Structure of the Y chromosome
- Evolution of Y chromosome from autosomes
- Genes on human Y chromosome
- SRY gene and sex determination
- Azoospermia factors
- Copy number variations
- Functions
- Y chromosome-linked disorders

7.1 Introduction

Y chromosome is an important chromosome that plays a crucial role in determination and differentiation of testes in male. Y chromosome has genes both testes specific and ubiquitous; thus, it also performs functions other than reproduction. Deletions, duplications, inversions, and other mutations are very common with Y chromosome due to

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absence of homologous pair and minimal crossing over in meiosis. Holandrically transmitted non-recombining region of Y (NRY) has made possible unraveling the mystery of human evolution. With only 1/6 the size of its partner X chromosome and merely 1/12 the number of genes that it carries, Y chromosome presents clear signs of a degenerated chromosome. We shall now describe the Y chromosome in detail.

7.2 Structural Components

Humans have two sex chromosomes – X chromosome and Y chromosome in male and two X chromosomes in female. The length of human Y chromosome is about 60 megabase (Mb) and represents about 2% of human genome (Murci and Fellous 2001). The Y chromosome is a small acrocentric chromosome and is placed in G group of human karyogram. Y chromosome has very short "p" arm (Yp) and relatively long "q" arm (Yq; see Fig. 7.1).

Y chromosome is one of the major contributors of sex determination in male. Based on the genetic deletion map, human Y chromosome is divided into 7 intervals – deletion interval 1 to 7 which are further subdivided into subintervals (see Fig. 7.2). Intervals 1, 2, and 3 are present on Yp; interval 4 lies at peri-centromere, while intervals 5, 6, and 7 are present on Yq (Vergnaud et al. 1986).

Cytogenetic banding study divides human Y chromosome into distinct regions – pseudoautosomal region (PAR) 1, 2, and 3, euchromatic regions, and heterochromatic region (see Fig. 7.2). PAR is the region which pairs with the respective region on X chromosome and undergoes exchange during meiosis. PAR 1 is 2771.47 kb (genomic coordinate Y:10,000–2,781,479) and is present at Yp terminal; PAR2 is 329.5 kb in size (genomic coordinate Y:56,887,902–57,217,415) and is present at Yq terminal. PAR 3 lies 700 kb away from PAR1 at Yp11.2 and is found in only 2% of general population. PAR3 shows unequal allelic recombination with its X homologue, i.e., Xq21.3 (Veerappa et al. 2013).

PAR1 and PAR2 comprise about 5% of the total Y chromosome (see Fig. 7.2). The rest 95% of Y chromosome comprises the NRY, also called male-specific Y (MSY) region, which includes both heterochromatic and euchromatic regions. The heterochromatic region lies at Yq12 locus on the distal end of Y chromosome. The heterochromatic region is genetically inert and comprises of mainly two extremely repetitive sequences – DYZ1 and DYZ2 – each having 5000 and 2000 copies, respectively. The length of the heterochromatic region varies in different populations due to

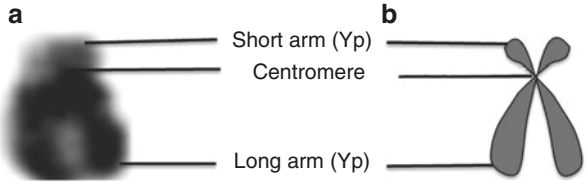

Fig. 7.1 (**a**) Unstained image of the Y chromosome taken from metaphase spread of male blood lymphocytes and (**b**) schematic diagram showing very short p arm and relatively long q arm of Y chromosome

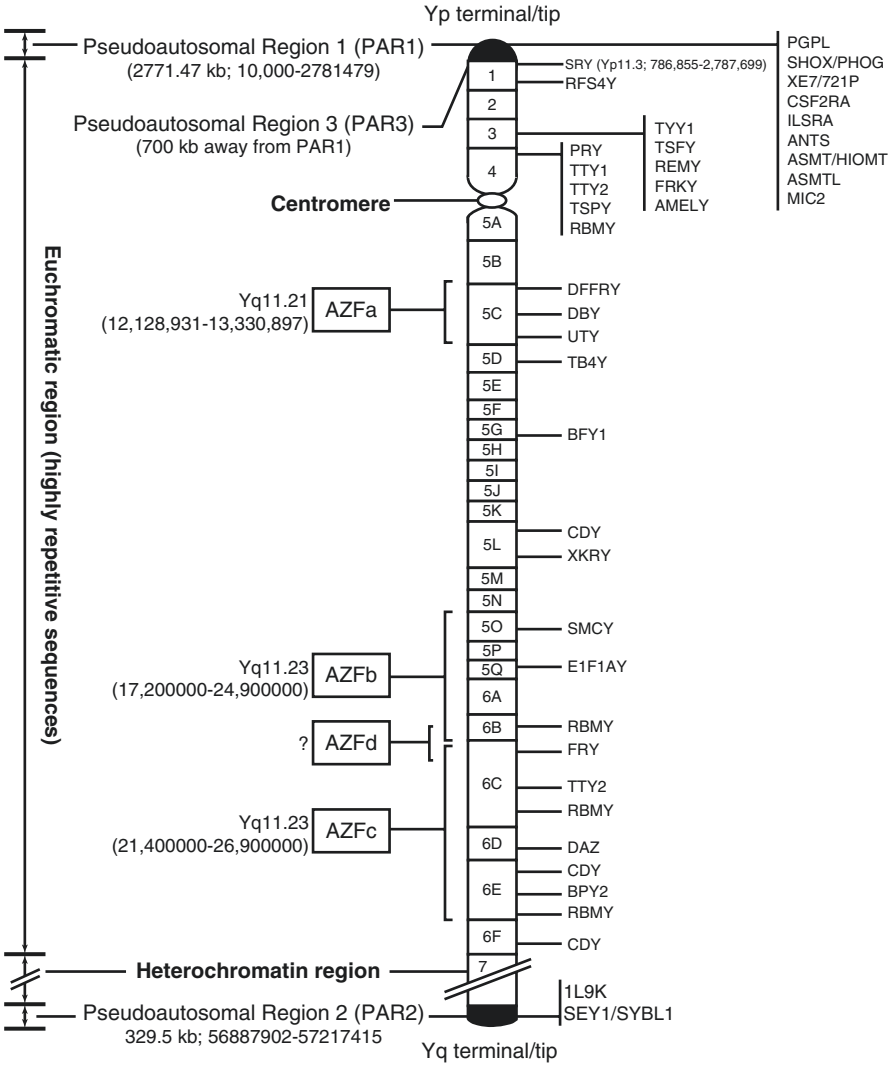

Fig. 7.2 Schematic diagram showing genetic deletion mapping dividing Y chromosome into 7 intervals. The candidate genes belonging to each region are shown on right; *AZFa–d* azoospermia factors (Adapted and modified from Murci and Fellous (2001))

copy number variations (CNVs). The euchromatic region of Y chromosome is present near the centromere of both arms. Many highly repetitive sequences are present in the euchromatic region in addition to several genes, having major biological roles like sex determination and spermatogenesis. The genes in the euchromatic region of Y chromosome belong to one of the three categories: X transposed, X degenerate, or ampliconic, depending upon the mode of evolution of the segment of Y to which they belong (Skaletsky et al. 2003). Different regions of Y chromosome as seen in fluorescent in situ hybridization (FISH) are shown in Fig. 7.3.

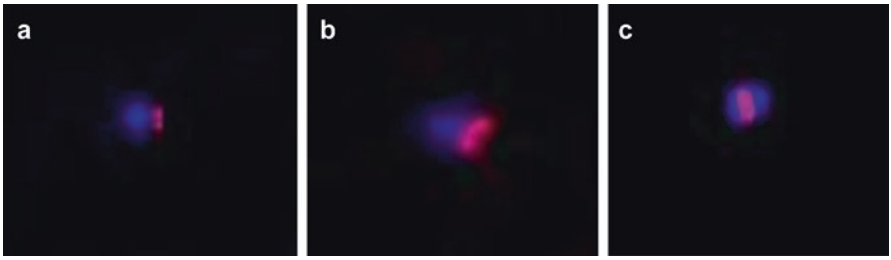

Fig. 7.3 Fluorescent in situ hybridization (FISH) images of chromosome Y (stained with DAPI: blue) is showing (**a**) SRY (*red*), (**b**) centromere (*red*), and heterochromatin region: (**c**) (*red*)

7.3 Evolution

The present form of human Y chromosome has evolved from autosomes and comprises only 3% of its ancestral genes (Skaletsky et al. 2003; Bellott et al. 2010). In the beginning, the changes leading to the formation of Y chromosome from autosomes were very fast, but have slowed down for past 25 million years (Hughes et al. 2012). When chromosome pairs recombine during meiosis in the germ cells, DNA is exchanged in such a way that the accumulated mutations get corrected via DNA exchange or recombination. The same process does not happen with the Y chromosome as it does not have counter pair except for the PAR regions which contribute only 5% of Y genome. Thus, degeneration might have occurred secondary to non-recombination leading to high mutation, inefficient selection, and genetic drift giving rise to the present form of Y (Graves 1995). The euchromatic region constitutes 156 transcription units known so far, together with 78 protein-coding genes which collectively encode 27 specific proteins. The transcription units belong to three types of sequences in the Y euchromatic region depending upon the source from which they are derived to become a part of Y, namely, X-transposed sequences, X-degenerate sequences, and ampliconic sequences (see Table 7.1 and Fig. 7.4).

X-transposed genes are derived from the genes on the X-linked region which, in turn, are derived from ancestral autosomes. X degenerate containing genes and pseudogenes are derived from autosomes (Watson et al. 1991). Ampliconic genes are the result of three converging processes:

(i) X-degenerate gene amplification (RBMY and VCY)
(ii) Autosomal gene transposition and amplification (DAZ)
(iii) Autosomal gene re-transposition and amplification (CDY)

The X-transposed sequences show 99% similarity to the X chromosome. The X-transposed region came to lie on human NRY/MSY around 3–4 million years ago after X to Y transition (see Fig. 7.4; Page et al. 1984; Mumm et al. 1997; Schwartz et al. 1998). Within the X-transposed segments of about 3.4 Mb, there are only two genes, both having homologues in Xq21.The nucleotide sequences of single copy MSY genes show 60–96% homology to their X-linked counterparts. Remarkably,

Table 7.1 Characteristics of three sequence classes in NRY/MSY euchromatic region

Sequence class	Evolutionary origin	Defining characteristic	Distribution	Total length (Mb)	No. of coding genes	No. of transcription units per Mb	No. of noncoding transcription units	Tissue expression
X transposed	Single transposition from X	99% identity to X	2 segments on Yp	3.4	2	0.6	0	TGIF2LX testis specific; PCDH11X in brain
X degenerate	Relics of ancient autosomes from which X and Y evolved	Genes or pseudogenes present as single copy and having X homologues	8 segments:2 on Yp; 6 on Yq	8.6	16, most expressed widely	2.2	4	Widely expressed
Ampliconic	Acquired from diverse sources, then amplified	Repetitive sequences with 99.9% similarity to MSY regions	7 segments: 2 on Yp; 7 on Yq	10.2	60, belonging to 9 families	13.3	74 (9 single-copy; 65 in l5 families)	Testis specific

Adapted and modified from Skaletsky et al. (2003)

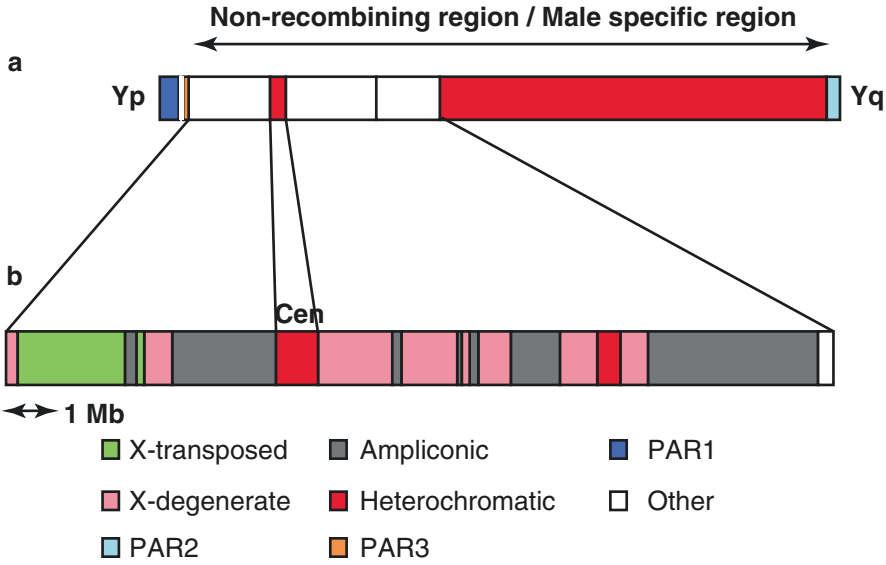

Fig. 7.4. Evolution of the Y chromosome: (**a**) whole Y chromosome, including the pseudoautosomal regions (*PAR 1, 2 and 3*) and the non-recombining region (NRY)/male-specific region (MSY) which includes euchromatic and heterochromatic regions. (**b**) Enlarged view of a 24-Mb euchromatic portion of the NRY, extending from the distal boundary of PAR1 on Yp to proximal boundary of the large heterochromatic region of Yq displaying the ways by which various parts of the Y euchromatic region are derived to finally become part of Y chromosome (Adapted and modified from Skaletsky et al. 2003)

all of the 12 universally expressed MSY genes are present in X-degenerate regions, and none of these genes have been recognized anywhere other than MSY. On the other side, out of the 11 MSY genes, which are expressed chiefly in testes, only one gene, the sex-determining region Y (SRY), is located in the X-degenerate region.

The third category of the euchromatic region is the ampliconic sequence which constitutes about 30% or 10.2 Mb of the MSY euchromatin. Ampliconic sequences present 99.9% similarity to other regions within the MSY. Such regions, extending over tens or hundreds of Kb and belonging to different families, are referred to as MSY-specific long repeat units. The amplicons are situated in seven segments scattered across 10.2 Mb length covering long arm and proximal short arm of the euchromatic region. Maximum genes are present in the ampliconic region, which includes both coding and noncoding genes (see Table 7.1). There are nine MSY-specific protein-coding gene families having different copy numbers ranging from two for VCY, XKRY, HSFY, and PRY; three for BPY2; four for CDY and DAZ; six for RBMY; around 35 CNVs for TSPY (Skaletsky et al. 2003). The copy numbers may vary in human populations. In contrast, all the nine gene families in the ampliconic region show highly restricted testis-specific expression (see Table 7.2).

Table 7.2 Genes of NRY/MSY euchromatic region

NRY/MSY sequence class	Gene name (symbol)	Number of copies	Homologous gene on X	Homologous gene on Autosome	Tissue expression
X transposed	TGF (beta)-induced transcription factor 2-like Y (TGIF2LY)	1	TGIF2LX	–	Testes
	Protocadherin 11 Y (PCDH11Y)	1	PCDH11X	–	Fetal brain, brain
X degenerate	Sex-determining region Y (SRY)	1	SOX3	–	Predominantly testes
	Ribosomal protein S4 Y isoform 1 (RPS4Y1)	1	RPS4X	–	Universal
	Zinc-finger Y (ZFY)	1	ZFX	–	Universal
	Amelogenin Y (AMELY)	1	AMELX	–	Teeth
	Transducin (beta)-like 1 protein Y (TBL1Y)	1	TBL1X	–	Prostate, fetal brain
	Protein kinase Y (PRKY)	1	PRKX	–	Universal
	Ubiquitin-specific protease 9 Y (USP9Y)	1	USP9X	–	Universal
	Dead box Y (DBY)	1	DBX	–	Universal
	Ubiquitous TPR motif Y (UTY)	1	UTX	–	Universal
	Thymosin (beta)-4 Y (TMSB4Y)	1	TMSB4X	–	Universal
	Neuroligin 4 isoform Y (NLGN4Y)	1	NLGN4X	–	Prostate, testes, fetal and adult brain
	Chromosome Y open reading frame 15A (CYorf15A)	1	CXorf15	–	Universal
	Chromosome Y open reading frame 15B (CYorf15B)	1	CXorf15	–	Universal
	SMC (mouse) homologue, Y (SMCY)	1	SMCX	–	Universal
	Translation-initiation factor 1A Y (EIF1AY)	1	EIF1AX	–	Universal
	Ribosomal protein S4 Y isoform 2 (RPS4Y2)	1	RPS4X	–	Universal

(continued)

Table 7.2 (continued)

NRY/MSY sequence class	Gene name (symbol)	Number of copies	Homologous gene on X	Homologous gene on Autosome	Tissue expression
Ampliconic	Testis-specific protein Y (TSPY)	~35	–	–	Testes
	Variable charge Y (VCY)	2	VCX		Testes
	XK-related Y (XKRY)	2	–	–	Testes
	Chromodomain Y (CDY)	4	–	CDYL	Testes
	Heat shock transcription factor Y (HSFY)	2	–	–	Testes
	RNA-binding motif Y (RBMY)	6	RBMX	–	Testes
	PTP-BL-related Y (PRY)	2	–	–	Testes
	Basic protein Y 2 (BPY2)	3	–	–	Testes
	Deleted in azoospermia (DAZ)	4	–	DAZL	Testes
Grand total		~78			

Adapted and modified from Skaletsky et al. (2003)

7.4 Genes on the Human Y Chromosome

Human Y chromosome has limited number of genes as compared to other chromosomes. The reduction in number of genes may have resulted from degeneration process during evolution (Graves 1995). The ancestral autosomal genes passed through X and Y chromosome to ultimately lie on NRY in present time (Bull 1983). Table 7.3 provides a summary of the genes present on NRY, PAR1, PAR2, and PAR3 of Y chromosome. The genes belonging to the NRY region can be further subdivided into two groups. The first group has genes which are expressed ubiquitously, exist as single copy having X homologues, and perform housekeeping functions. The second group includes genes that have testis-specific expression performing additional specialized functions and exist in multiple copies except the SRY gene which is present in single copy. The findings regarding X homologues of NRY genes are worth mentioning which provides an alternate answer for gene dose compensation. The NRY genes have escaped X inactivation and encode functionally interchangeable proteins (Lahn and Page 1997).

7.4.1 Sex-Determining Region Y (SRY) Gene

The SRY gene is present on Yp11.3 (genomic coordinate Y:786,855–2,787,699) and is responsible for testis determination (Sinclair et al. 1990). The SRY protein has 204 amino acid sequence encoded by a single exon spanning the SRY gene. The protein

Table 7.3 Genes on the human Y chromosome

Gene name (symbol)	Location (genomic coordinate)	Associate pathology/function	References
Phosphatidylinositol-specific phospholipase C, X domain containing 1 (PLCXD1)	PAR1 (Y:142,991–170,020)	Unknown	Kimura et al. (2006)
GTP-binding protein 6 (GTPBP6)	PAR1 (Y:171,426–180,887)	Unknown	Gianfrancesco et al. (1998)
Protein phosphatase 2, regulatory subunit B (PPP2R3B)	PAR1 (Y:333,933–386,955)	Regulates DNA replication. Overexpression causes G1 cell cycle arrest	Yan et al. (2000)
Short stature homeobox (SHOX)	PAR1 (Y:624,344–659,411)	Transcription factor associated to short stature syndromes	Rao et al. (1997)
Cytokine receptor-like factor 2 (CRLF2)	PAR1 (Y:1,264,869–1,281,529)	Receptors that bind TSLP cytokine; enhances dendritic cell maturation and $CD4^+$ T-cell proliferation	Al-Shami et al. (2005)
Colony-stimulating factor 2 receptor, alpha (CSFR2Rα)	(Y:1,337,701–1,378,827)	Receptor that binds granulocyte-macrophage colony-stimulating factor (GM-CSF); regulates eosinophil and macrophage development in the bone marrow and cell viability in human embryos	Sjoblom et al. (2002)
Interleukin 3 receptor, alpha (IL3RA)	(Y:1,405,509–1,451,582)	Receptors for interleukin 3	Kremer et al. (1993)
Solute carrier family 25 member A6 (SLC25A6) or ANT3, ANT3Y, MGC17525	PAR1 (Y:1,455,045–1,460,998)	A member of the ADP/ATP translocase family, which has a potential role in Th cell survival and immune cell homeostasis	Jang and Lee (2006)
Acetyl serotonin O-methyltransferase-like (ASMTL)	(Y:1,403,139–1,453,795)	Unknown	Ried et al. (1998)

(continued)

Table 7.3 (continued)

Gene name (symbol)	Location (genomic coordinate)	Associate pathology/function	References
Purinergic receptor P2Y, G-protein-coupled 8 (P2RY8)	(Y:1,462,572–1,537,506)	A member of the purine nucleotide G-protein coupled receptor gene family	Cantagrel et al. (2004)
CXYorf3 (XE7, XE7Y, DXYS155E, MGC39904, B lymphocyte surface antigen 721P, X escapee, CCDC133)	(Y:1,591,593–1,602,520)	Alternative splicing regulator	Mangs et al. (2006)
Acetyl serotonin O-methyltransferase (ASMT) or HIOMT, ASMTY, HIOMTY	(Y:1,595,455–1,643,081)	Catalyzes final reaction in melatonin synthesis	Slim et al. (1993)
Dehydrogenase/ reductase (SDR family) X linked (DHRSXY)	PAR1 (Y:2,087,547–2,369,015)	Encodes an oxidoreductase of the short-chain dehydrogenase/ reductase family	Gianfrancesco et al. (2001)
Zinc finger, BED-type containing 1 (ZBED1)	(Y:2,486,414–2,500,967)	Transposition of other transposable elements	Esposito et al. (1999)
CD99: CD99 molecule (MIC2)	PAR1 (Y:2,691,187–2,741,309)	Cell-surface molecule involved in T-cell adhesion and activation of death pathway in T cell	Pettersen et al. (2001)
XG blood group (XG)	PAR1 (Y:2,751,820–2,816,500)	Encodes cell-surface antigen	Ellis et al. (1994)
Sex Reversal/ determining region Y (SRY[a])	NRY (Yp:1A1A;Y:786,855–2,787,699)	Sex reversal	Sinclair et al. (1990)
Ribosomal protein S4,Y(RPS4Y)	NRY (Yp:1A1B; Y:2,709,623–2,734,997)	Turner syndrome?	Fisher et al. (1990)
Zinc-finger Y (ZFY)	NRY (Yp:1A2; Y:2,934,416–2,982,508)	Turner syndrome?	Page et al. (1987)
Protein kinase, Y (PRKY)	NRY (Yp:3C-4A; Y:7,273,972–7,381,547)	Unknown	Shiebel (1997)
Testis transcript, Y1(TTY1[a])	NRY (Yp:4A; Y:9,753,156–9,774,289)	Unknown	Reijo et al. (1995)
Testis sepsis protein, Y (TSPY[a])	NRY(Yp:3C + 5; Y:410,723–413,797)	Gonadoblastoma	Arnemann et al. 1987
Amelogenin, Y (AMELY)	NRY (Yp:4A; Y:6,865,918–6,911,937)	Unknown	Nakahori et al. (1991)
Putative tyrosine phosphate protein-related Y (PRY[a])	NRY (Y:4A, 6E; Y:22,484,280–22,515,543)	Infertility?	Reijo et al. (1995)

Table 7.3 (continued)

Gene name (symbol)	Location (genomic coordinate)	Associate pathology/function	References
Testis transcript, Y2 (TTY[a])	NRY Y:4A-6C	Unknown	Reijo et al. (1995)
Ubiquitin-specific protease (or *Drosophila* fat-facets related, Y) (USP9Y) or DFFRY	NRY (Yq:5C; Y:14,813,160–14,972,768)	Azoospermia?	Lanh and Page (1997)
DEAD box, Y (DBY)	NRY (Yq:5C; Y:12,904,108–12,920,478)	Infertility?	Lanh and Page (1997)
Ubiquitous TRY motif, Y (UTY)	NRY (Yq:5C; Y:13,233,920–13,480,670)	Infertility	Lanh and Page (1997)
Thymosin?4, Y isoform (TB4Y)	NRY (Yq:5D; Y:13,703,567–13,706,024)	Infertility	Lanh and Page (1997)
Basic protein,Y1 (BPY1[a])	NRY (Yq:5G; Y:13,985,772–13,986,512)	Turner?	Reijo et al. (1995)
Chromodomain, Y (CDY)	NRY (Yq:5 L, 6F; Y:8,813,079–8,815,071)	Infertility?	Lanh and Page (1997)
XK-related, Y (XKRY[a])	NRY (Yq:5 L; Y:17,768,980–17,770,560)	Infertility?	Reijo et al. (1995)
RNA-binding motif, Y (RBM[a])	NRY (Yp + q; Y:21,534,902–21,561,014)	Infertility?	Ma et al. (1993)
Selected mouse cDNA, Y (SMCY)	NRY (Yq:5P; Y:19,705,415–19,744,939)	Unknown	Agulnik et al. (1994)
Translation-initiation factor 1A,Y (E1F1AY)	NRY (Yq:5Q; Y:22,737,611–22,755,040)	Infertility?	Lanh and Page (1997)
Deleted in azoospermia (DAZ[a])	NRY (Yq:6F; Y:25,365,622–25,437,497)	Infertility?	Reijo et al. (1995)
Variably charged protein, Y2 (VCY2)	NRY (Yq:6A; Y:22,984,263–23,005,465)	Infertility	Reijo et al. (1995)
Interleukin 9 receptor (IL9R)	PAR2 (Y:59,330,252–59,343,488)	Unknown	Vermeesh et al. (1997)
Synaptobrevin-like 1 (SYBL1)	PAR2 (Y:57,067,800–57,130,289)	Unknown	Kermouni et al. (1995)
Human-sprouty 3 (HSPRY3)	PAR2 (Y:59,100,457–59,115,123)	Unknown	Ciccododicola et al. (2000)
Chromosomes X And Y Open Reading Frame 1 (CXYORF1)	PAR2 (Y:156,020,826–156,025,710)	Unknown	Ciccododicola et al. (2000)
Protocadherin 11 Y linked (PCDH11Y)	PAR3 (Y:4,868,267–5,610,265)	Unknown	Veerappa et al. (2013)
TGFB-induced factor homeobox 2-like, Y linked (TGIF2LY)	PAR3 (Y:3,579,085–3,580,041)	Unknown	Veerappa et al. (2013)

Adapted and modified from Murci and Fellous (2001)
[a]Testis-specific genes or families

comprises of nucleic acid-binding domain and, thus, has a role in regulating gene expression. SRY gene initiates testis development as it differentiates the bipotential gonad to testicular pathway. Many other genes and loci interact with SRY protein, such as SOX-9, steroidogenic factor 1 (SF-1), and Wilm's tumor gene 1 (WT-1).

7.4.2 Azoospermia Factors

Azoospermia factors (AZFs) are the spermatogenesis loci present in the Yq11.2 region. The types of AZFs are AZFa, AZFb, and AZFc (see Fig. 7.2). AZFa (Yq11.21; genomic coordinate Y: 12,128,931–13,330,897) is located on the anterior side of deletion interval 5C.The size of the AZFa region is around 1 Mb. AZFb (Yq11.23; genomic coordinate Y:17,200,000–24,900,000) covers the region from deletion interval 5 to deletion interval 5O to 6B. AZFb covers 1–3 Mb DNA. AZFc (Yq11.23; genomic coordinate Y:21,400,000–26,900,000) is present on deletion interval 6C to 6E and covers 3.5 Mb DNA. Another region AZFd is described amid AZFb and AZFc, but existence of this region needs further verification (Kent-First et al. 1999). In all, 12 genes have been defined in AZF regions (Reijo et al. 1995).

7.4.2.1 AZFa

The AZFa region contains three genes (Lahn and Page 1997; Mazeyrat et al. 1998; Sargent et al. 1999). The first known gene in the AZFa region is DFFRY (*Drosophila* fat facet-related Y), also known as USP9Y (ubiquitin-specific protease 9; Mazeyrat et al. 1998; Brown et al. 1998). The DFFRY gene is located at Yq11.21 (genomic coordinate Y: 12,701,231–12,860,844). DFFRY gene is ubiquitously expressed and exists in single copy. It has an X homologue which escapes X inactivation and acts as a C-terminal ubiquitin hydrolase without encoding for RNA-binding protein (Lahn and Page 1997; Brown et al. 1998). USP9Y occupies less than half of the AZFa interval (Sargent et al. 1999). The other two X-Y homologous genes present in AZFa are DBY (dead box on the Y), located at Yq11.221 (genomic coordinate Y:12,904,108–12,920,478), and UTY (ubiquitous TPR motif on the Y), located at Yq11.221 (genomic coordinate Y:13,233,920–13,480,673; Lahn and Page 1997; Mazeyrat et al. 1998). AZFaT1 is another unique sequence described in AZFa (Sargent et al. 1999). The genes in AZFa may work singly or in combination with USP9Y. Absence of a single gene or combination of genes in cases of AZFa deletion has been associated with spermatogenic disruption, in particular with Sertoli cell-only syndrome or azoospermia leading to male infertility (Vogt et al. 1996; Sargent et al. 1999).

7.4.2.2 AZFb

AZFb has two genes – RBMY (RNA-binding motif on the Y) located on Yq11.223 (genomic coordinate Y:21,534,902–21,561,014) and EIF1AY (translation-initiation factor 1A, Y isoform) located on Yq11.223 (genomic coordinate Y:20,575,711–20,593,154). RBMY was identified and cloned from deletion interval 6 (Ma et al. 1993). Initially, it was proposed to have two motifs – YRRM1 and YRRM2 (Y-specific RNA recognition motif). Later on, it was found that there is actually a family of 20–50 genes and

pseudogenes extending from Yp to Yq arm with a lot of genes concentrated in AZFb (Prosser et al. 1996; Elliott et al. 1997). So, the name changed from YRRM to "RBMY gene family" (Vogt et al. 1997). The genes belonging to RBMY gene family are divided into six subfamilies (Chai et al. 1997, 1998). The only actively transcribed gene is RBMY-I with majority of functional copies present in deletion interval 6B and so is the candidate gene in AZFb (Vogt et al. 1997). The protein encoded by RBMY gene has a single RRM (RNA recognition motif)-type RNA-binding domain at the N-terminal and four 37-amino acid repeats at the C-terminal. The C-terminal domain has a serine-arginine-glycine-tyrosine sequence and, so, is named SRGY box. All eutherians have multiple copies of RBMY gene (Delbridge et al. 1997). The active X homologue of the gene has retained widespread functions, while Y homologue has male-specific role in spermatogenesis (Delbridge et al. 1999; Mazeyrat et al. 1999). In accordance with its role in spermatogenesis, the RBMY genes are expressed only in the testicular germ cells (Elliott et al. 1997). Big AZFb deletions are known to cause azoospermia, while microdeletions are related to oligozoospermia and a variety of other infertile phenotypes. But, the exact role of RBMY in male germ cell development is still unclear because differential functions are associated with pre-mRNA splicing and variations in spatial localization in different testicular germ cells (Elliott et al. 1998). EIF1AY has ubiquitous expression and codes for Y isoform of eukaryotic translation-initiation factor, eIF-1A which also has a X homologue (Lahn and Page 1997). No specific deletion of this gene is known that could suggest its role in spermatogenesis. But, EIF1AY definitely plays some role in AZFb phenotype as it has many testis-specific transcripts along with the ubiquitously expressed transcripts (Lahn and Page 1997).

7.4.2.3 AZFc

The AZFc region has seven gene families performing different roles in spermatogenesis. The candidate gene of the AZFc region is DAZ (deleted in azoospermia) located on Yq11.223, deletion interval 6 (genomic coordinateY:23,129,355–23,199,123). DAZ belongs to a multigene family. Several copies of DAZ gene are present in the AZFc region of the Y chromosome (Saxena et al. 1996; Vogt et al. 1997; Glaser et al. 1998; Yen 1998). The DAZ gene has structural similarity with RBMY. DAZ gene is a 42 kb gene comprising 16 exons (Reijo et al. 1995; Saxena et al. 1996). There is individual variation in copy number and order of DAZ repeats (Yen et al. 1997). DAZ also has testicular germ cell specific expression (Menke et al. 1997; Habermann et al. 1998; Lee et al. 1998; Ferlin et al. 1999). Deletion of DAZ gene has been associated with spermatogenic defects (Reijo et al. 1995).

7.4.2.4 AZFd

So far, no gene has been described in the AZFd region. However, the DYS237 locus of AZFd may have some genes which play a role in spermatogenesis as predicted by deletion studies (Muslumanoglu et al. 2005). The length of deleted segment may vary. The most commonly observed deletion spans the region between the STS marker (SY153) in AZFd and the junction of euchromatic and heterochromatic regions. Microdeletions specific to AZFd have been shown to cause mild oligozoospermia or normal sperm count with defective sperm morphology (Kent-First et al. 1999).

7.5 Copy Number Variations (CNVs)

Chromosomal rearrangements can result in deletions, duplications, or unbalanced translocations which subsequently result in inappropriate gene dosage. Meiotic nondisjunction events in physiologically normal carriers of balanced translocations may also lead to a disturbance of gene dosage in offspring. Most of the rearrangements occur in specific regions of the genome, suggesting specific mechanisms causing these modifications. CNVs are submicroscopic DNA segments of 1 kb or more that are duplicated or deleted in the genome (Lee et al. 2007). CNVs can be pathogenic if they cause overt disease or benign if they predispose to disease or apparently have no effect. CNVs lie at the interface between microscopically visible rearrangements and point mutations; these are increasingly being investigated using microarray methods. Recent studies have shown that CNVs may affect around 20% of human genome. Currently, we are working on genotype-phenotype corelation in male infertility. Our initial findings indicate that CNVs of sex chromosomes, in particular of PARs, are more frequent with azoospermia (ongoing work; Halder 2016).

7.6 Functions

The Y chromosome has many functions to its credit that are restricted to the NRY. The characteristic roles of Y chromosome in humans include sex determination and development as well as maintenance of male gonads, including germ cells. Because Y chromosome is present only in males and is transmitted holandrically, it stores information on human evolution because the genes on the NRY region have never undergone recombination and are transmitted vertically as it is over generations (Murci and Fellous 2001).

7.7 Y-Linked Holandric Traits

Y-linked traits are controlled by alleles present on Y chromosome. Since only males have Y chromosome, Y-linked traits are passed from father to son. Approximately three dozen Y-linked traits have been discovered, and one such trait is hairy ears (Murci and Fellous 2001).

7.8 Y Chromosome-Linked Disorders

Mutations or deletions in Y chromosome result in Y-linked disorders, such as mutation in SRY, which results in defective testicular development, and deletion in the AZF region results in azoospermia. Protein encoded by AZF genes has a crucial role in germ cell development.

7.8.1 Defective Y Chromosome

Deleted SRY, incomplete Y, or fragmented Y may present as feminine phenotype, ambiguous genitalia, or infertility. As a result, there is defective testicular development along with defective internal and/or external male genitalia. In conditions of minimal or nonfunctioning Y fragment, the subject is usually a female having the features of mixed gonadal dysgenesis or Turner syndrome (Chang et al. 1990).

7.8.2 XX Male

The XX male syndrome is a rare genetic disorder. The phenotype is a variable that ranges from a severe impairment of external genitalia to a normal male phenotype with infertility. The genotype generally results from an unequal crossing over between the short arms of the sex chromosomes X and Y.

We observed a 38-year-old patient presented to us with concern of infertility. Physical examination and laboratory investigations showed normal external male genitalia with hypogonadism, gynecomastia, and glaucoma. The patient was azoospermic with high gonadotropin levels, low anti-Mullerian hormone (AMH), and low inhibin B levels. Karyotyping revealed 46, XX with absence of Y chromosome. FISH and PCR showed presence of SRY gene (see Fig. 7.5). Testicular fine-needle aspiration cytology (FNAC) revealed Sertoli cell-only syndrome (Jain et al. 2013).

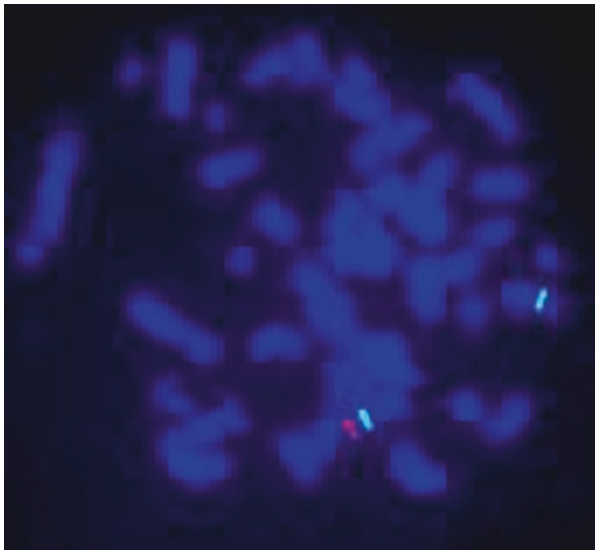

Fig. 7.5 Fluorescent in situ hybridization (FISH) image by using triple probe – *green* (X centromere), *red* (SRY), and yellow (Y centromere) signals. Two green signals indicate two centromeres of X chromosome. Absence of yellow signal indicates absence of Y centromere

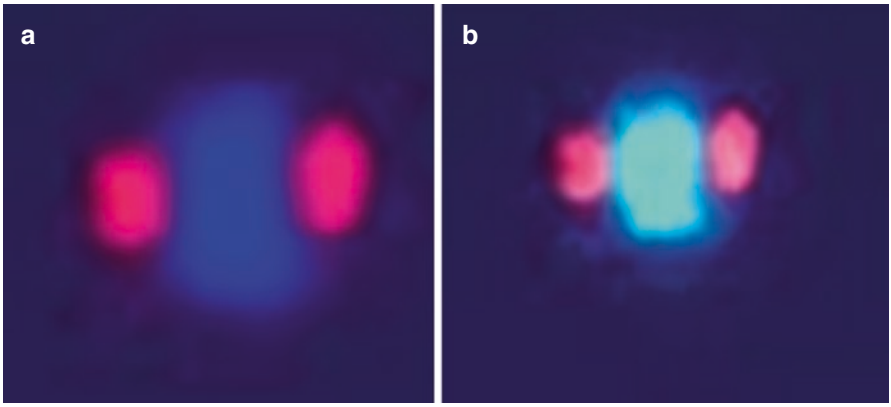

Fig. 7.6 Fluorescent in situ hybridization (FISH) image of Y dicentric chromosome: (**a**) CY3 (*red*) labeled Y centromere probe and DAPI stain showing two centromeres at the ends of rearranged Y chromosome; (**b**) FITC (*green*)-labeled Yqh probe and CY3 (*red*)-labeled Y centromere probe showing two centromeres (*red*) and in between heterochromatin region (*green*) of Y chromosome

7.8.3 Dicentric Y Chromosome

Dicentric Y chromosome is usually considered unstable since inappropriate position of two centromeres on metaphase spindle can cause bridge formation in anaphase. In some cases, if centromeres are close to each other, they can act as monocentric elements. In such situations, they replicate as normal chromosomes (Sears and Camera 1952; Darlington and Wiley 1953). Dicentric chromosomes are perhaps the most frequently encountered example of structural rearrangements of the Y chromosome. Several genes exist as multiple copies in the dicentric Y chromosome.

Dicentric Y chromosome (see Fig. 7.6) formation may occur in three ways: (1) by a break in Yp and reunion of the proximal ends of chromatid in meiosis I, resulting in a dicentric chromosome following meiosis II and the reduction of the centromere; (2) by a break in Yp or Yq followed by reunion of sister chromatid strands leading to duplication deficiency of short or long arm of Y chromosome; and (3) by breaks in either arm of the two Y chromosomes in an XYY individual, followed by exchange. The former two are the most likely mechanisms for the origin of the dicentric Y (Cohen et al. 1973).

7.8.4 Yqh Polymorphism and Inversions

The Y chromosome contains a major proportion of segmental duplication and shows cytogenetically observable structural polymorphisms such as length variation and inversions (Bobrow et al. 1971; Verma et al. 1978; Verma et al. 1982a; Bernstein et al. 1986; Skaletsky et al. 2003). The former comprises large Y (Yq+)

and small Y (Yq-) and the latter includes pericentric and paracentric inversions. Pericentric inversion is the rearrangement in which a segment, including the centromere, is rotated, while in paracentric inversion, the rotated segment does not include centromere. The Y chromosome is more polymorphic in the Asians (3.37%) and Hispanics (1.82%) compared to the Whites or Blacks (Hsu et al. 1987).

Y chromosome varies in length in different racial groups (Cohen et al. 1966). Variable length of Y chromosome has also been documented with different clinical conditions such as psychological disorders, Down syndrome, abnormal embryo development, birth complications, and bad obstetric history (Funderburk et al. 1978; Genest 1979; Verma et al. 1982a; Podugolnikova and Blumina 1983; Videbech et al. 1984; Minocherhomji et al. 2009).

The pericentric inversion of Y chromosome (invY) is familial (Solomon et al. 1964; Jacobs et al. 1964; Verma et al. 1982b). The incidence of invY ranges from 1 to 2 per 1000 male fetuses with an average of 1.15 per 1000 males (Shapiro et al. 1984). The incidence of invY in various populations has been studied worldwide (Bhasin 2005). 30.5% of invY has been reported in the immigrant Gujarati Muslim community which originated from Surat and settled in South Africa (Bernstein et al. 1986). Such type of polymorphic frequency of trait presents an example of random genetic drift occurring in reproductively isolated populations that follows rigid endogamy and without any reproductive abnormality. Other studies have shown association between pericentric inversion in different human chromosomes and congenital anomalies, repeated fetal loss, mental retardation, and infertility, possibly predisposing inter-chromosomal effect and nondisjunction (Krishna et al. 1992; Gardner and Sutherland 1996).

7.8.5 Gonadoblastoma

Gonadoblastoma is a rare benign tumor but can be potentially malignant (Scully 1953, 1970). Patients with disorders of sex development are at higher risk of developing gonadoblastoma. Two factors that predict development of gonadoblastoma are (1) presence of Y chromosome or a part of Y chromosome and (2) abdominal gonads. However, a limited number of cases of gonadoblastoma have been reported in patients with a 46,XX karyotype (Esin et al. 2012). The gene responsible for gonadoblastoma is gonadoblastoma locus on Y chromosome (GBY) which functions as an oncogene in conditions of dysgenetic gonads (Scully 1953). Studies from sex-reversed and gonadoblastoma patients reveal the position of GBY locus close to centromere of Y chromosome (Tsuchiya et al. 1995). The GBY locus has many genes. RNA-binding motif (RBM), protein tyrosine phosphatase (PTP) BL-related Y (PRY), amelogenin Y (AMELY), testis transcripts Y1 and Y2 (TTY1 and Y2), and protein kinase Y (PRKY) are some of known genes present in this locus.

Key Questions

Describe the euchromatin and heterochromatin regions of the Y chromosome.
What are the differences between X-linked and X-degenerate genes?
Explain briefly the evolution of Y chromosome from autosomes.
Describe the Azoospermic factor (AZF) region.
Describe the part of Y chromosome involved in Male fertility.
Name the Y-linked diseases.

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