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Review Article

**GENETIC INVESTIGATION AT AZOOSPERMIA FACTOR  
REGION FOR MALE INFERTILITY**Mili Nailwal<sup>1</sup>, Jenabhai B. Chauhan<sup>2\*</sup>

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Email: [jenabhaichauhan@aribas.edu.in](mailto:jenabhaichauhan@aribas.edu.in)/[jbc109@gmail.com](mailto:jbc109@gmail.com)**Abstract:**

*Due to globally increasing problem of infertility and its effect in the life of affected couple's, it is the biggest challenge and an urgent need to minimize this reproductive problem by advanced molecular genetics tools. The extent of microdeletions may affect the degree of spermatogenesis. Y chromosome microdeletion was found to have a prognosis value in the study of infertility, in terms of both the clinical management and the study of spermatogenesis impairment. One of the reason for screening Y-chromosome microdeletion is the possibility of vertical transmission of the Y-chromosome defect to the son conceived by assisted reproduction. With the development of intra-cytoplasmic sperm injection (ICSI), many of the natural selection barriers of fertilization are bypassed. Thus, defective sperms that do not have a chance to fertilize an oocyte in vivo might be able to do so after ICSI treatment. Routine screening of the AZF deletions is, therefore, important for patient counselling before ICSI treatment.*

**Keywords:** *Y-chromosome, Male infertility, Y-chromosome microdeletion, AZF region, Genetic evaluation, etiology of male infertility.*

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**INTRODUCTION:**

Worldwide, the incidence of male infertility is estimated that one in seven couples have problems in conceiving. This incidence is similar in many countries independent of the level of the country's development [1,2]. Infertility is defined as an inability to conceive or produce offspring according to WHO, 1992 manual [3]. The lower reference limit for Time to pregnancy (TTP) is twelve months according to WHO [4] and infertility is conceptualized as a major crisis in life. Infertility is a major health problem affecting approximately 15% of couples trying to have a child [5]. Being a parent and having a family is the primary requirement of all people in their adulthood. When it changes in infertility, it is truly a very painful struggle emotionally, psychologically and socially. Earlier, it was believed that women bear the sole responsibility for the failure to conceive in infertile couple. However, in reality infertility is not just limited to women alone. Male factor infertility is responsible for approximately 50% of infertile couples [6]. A noticeable amount of male with infertility are affected either by azoospermia which means lack of spermatozoa in ejaculation or oligozoospermia men with low sperm count below 15 million/mL of ejaculation. Male infertility has been associated with a number of non-genetic and genetic factors [7]. In male infertility, genetic factors have aid to many types of physiological processes considering hormonal homeostasis, spermatogenesis and sperm quality [8]. It was determined that sex determination is controlled by the *SRY* gene located on Y chromosome [9], but this concept changed in past few decades when another important function (the control of spermatogenesis) was discovered and many genes were mapped to the Y chromosome [10,11]. The most common genetic cause is microdeletions in azoospermia factor (AZF) region on Y chromosome [12]. Deletions in AZF region of the Y chromosome are associated with spermatogenic failure and is represented by most frequent genetic cause of azoospermia and severe oligozoospermia [13]. The development of intra-cytoplasmic sperm injection (ICSI) as an efficient therapy for severe male infertility has become an effective treatment for the majority of male reproductive tract deficiencies [14]. The study of Y chromosome microdeletions is important because of the potential for transmission of genetic abnormalities from infertile male to the offspring [15], as these advance techniques bypass physiological mechanisms associated to fertilization. From the bioethical point of view, it is important to inform the infertile couple about the potential genetic risks inherent by assisted reproduction [16]. The objective of this review is to discuss the most common causes of male infertility and the potential

problems associated with the Y-chromosome microdeletions.

**Milieu of Male Infertility**

In 2010, it is estimated that 48.5 million couples worldwide were infertile [17]. Infertility is a critical element of reproductive health and can be classified as primary or secondary infertility. Primary infertility is when a couple faces challenges when a female is unable to conceive a child either due to inability to become pregnant or carry a pregnancy to a live-birth. The causes of infertility can be both physical as well as emotional. Secondary infertility is when a female is unable to bear an offspring either due to inability to carry a pregnancy to live birth following either a previous pregnancy or ability to carry a pregnancy to a live birth.

**Social Impact of Infertility**

Parenthood is most important transition in adult life for both the partners. The pressure of the non-fulfilment of a wish for parenthood has been associated with emotional shriek such as anger, depression, anxiety, marital problems and feeling of worthlessness. Partners may become more anxious to conceive, ironically increasing sexual dysfunction and social isolation. Couples experience disgrace, sense of loss and diminished self-esteem during their infertility period [18]. In closed social groups, a degree of rejection may cause considerable stress and disappointment. Thus, infertility is having social, physical and psychological effects on the couple.

**Prevalence**

Prevalence of infertility varies depending on the various factors like reproductive capacity of both male and female, time span involved in failure to conceive, other environmental factors etc. also prevalence varies from country to country (Table 1). If we look at the overall prevalence of microdeletion in the AZF region, maximum deletion is observed in AZFc sub-region particularly DAZ gene dysfunction which may be considered to account for an extensive portion of cases of infertility in men.

**Etiology of Male Infertility**

The etiology of male infertility can be related to a wide range of genetic and non-genetic conditions.

**Non- Genetic Causes of Male Infertility**

Non-genetic causes of male infertility represents hypogonadotropic hypogonadism, coital disorders, orchitis, testis trauma, torsions, iatrogenic forms, hormonal, varicoceles and immunological causes [38]. It is also associated with an increasing number of proven risk factors, including exposures to occupational, lifestyle or environmental factors [39].

*Hormonal Causes:* Increased level of luteinising hormone (LH) and follicle-stimulating hormone (FSH) and low level of gonadal steroids cause gonadal failure and finally infertility. Increased concentrations of LH in male can result in hypergonadotrophic hypogonadism (HGH) which could be due to several causes including Kallmann's syndrome, pituitary trauma, pituitary tumour and consumption of anabolic steroid. In male infertility, HGH is rare and the disorder can be classified as congenital or acquired [40]. Hyperprolactinemia is a type of HGH caused by excessive secretion of prolactin [41].

*Physical causes:* Variety of physical problems can lead to male infertility. These problems either interfere with the sperm production or disrupt the migration of sperm traveling pathway from the testes to the tips of penis. It can happen due to varicocele, cryptorchidism, hypospadias, damaged sperm ducts, injury, torsion or obstruction in the reproductive tract (obstructive azoospermia).

*Exposure to chemicals and environmental causes:* Occupational exposure to some agrochemicals /pesticides, metals and solvents can affect fertility in men. Number of chemicals has been implicated as reproductive toxicants. The increased concentration of air pollutant which exist in the blood, urine and semen of exposed men allowed for sperm function tests have shown that high level of lead in semen samples lower the ability of the sperm to bind, penetrate and fertilise the egg. It was also reported that in young men, alterations in sperm quality after exposure to increased level of air pollution, without any changes in sperm numbers [39]. The use of agrochemicals suggest that it may reduce the semen quality in fertile men [42]. Increased attention is given to developing countries regarding the damaging effects of environmental chemical agents on male reproduction [43]. Certain environmental chemicals exposure such as di-bromochloro-propane, a pesticide had marked effect on sperm count leading oligozoospermia and azoospermia were also reported in exposed workers [44,45].

*Immunological causes:* Naturally occurring antisperm antibodies (ASA) is the cause of male infertility in infertile men reported by Rumke and Wilson, 1954 [46,47]. Impairment of sperm penetration through the cervical mucus occur due to naturally occurring antisperm antibodies in men are relative cause of infertility [46,47,48].

### **Genetic Causes of Male Infertility**

Genetic causes in infertile men may have phenotypical abnormalities or sperm abnormalities. A genetic factor plays a significant role in evolution and management of male infertility. The common genetic disorders that are associated with male infertility are reviewed below.

*Klinefelter's syndrome:* It is a genetic condition where each cell in the human body has 48 chromosomes with an additional X chromosome i.e. man with Klinefelters syndrome have one Y and two X chromosomes occur due to non-disjunction of the X chromosome during meiosis. This syndrome is found in approximately 1 in 500 males. There are several mosaic forms of Klinefelter's syndrome but most cases are of the nonmosaic form, 47, XXY and mostly detected in non-obstructive azoospermia [49]. The classical phenotype of men with Klinefelter's Syndrome is characterized by small and hard testicles, micropenis, tall eunuchoid body, low level of testosterone, thin facial and pubic hair, sterility and mild to moderate cognitive deficits [50]. 46, XX males a variant of Klienfilter's syndrome with small testes and associated with infertility. There is translocated portion of the Y-chromosome carrying the SRY gene [49]. As there is no AZF region, these patients are azoospermic. Jacob's syndrome (47, XYY) is another problem where spermatogenesis ranges between normal to severely impair. Men with Klinefelter's syndrome are mostly severe oligozoospermic or azoospermic.

*Kallmann syndrome:* This syndrome is a hormonal disorder in which there is a lack of GnRH secretion leads to testicular insufficiency [51]. Kallmann syndrome, inherited in an X-linked fashion, is caused by mutation in KAL1 gene, which produces a cell adhesion molecule [52].

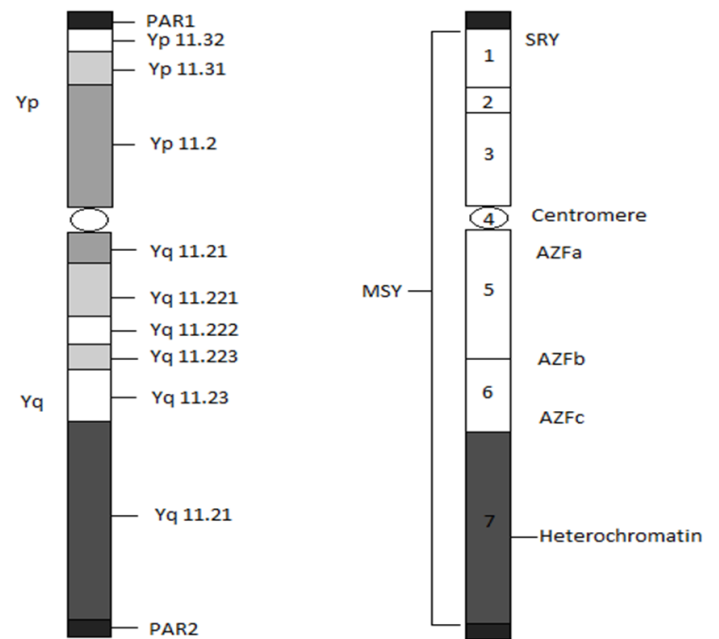
*Congenital bilateral absence of vas deference (CBAVD):* CBAVD arise due to mutation in cystic fibrosis transmembrane conductance regulator (CFTR) gene which encodes CFTR protein is required for maintaining proper sodium-chloride balance in epithelial secretions. This balance is necessary to maintain the viscosity and fluidity of these secretions [49,53]. The CFTR gene is mapped to short arm of chromosome 7. It is found in approximately 1% in infertile males and 10%-15% of azoospermic men [49]. The clinical features of the patients with CBAVD includes normal size and full testes, normal caput epididymis caused by efferent ducts that are enlarged with sperm, a presence or absence of distal two-thirds of the epididymis and a bilateral absence of the vas deferens. Ejaculation is low in volume (0.5 mL), acidic, absence of fructose and absence of seminal vesicle fluid because of

degeneracy, dysfunctional or absent seminal vesicles [53].

**Y-chromosome microdeletion:** In 1976, Tiepolo and Zuffardi were the first to publish the relationship between deletions on the Y chromosome and azoospermia, and concluded that factors controlling human spermatogenesis i.e. azoospermic factor (AZF) located on the long arm of Y chromosome (Yq11) [11]. Y chromosome microdeletions may be detected in 10% - 15% of azoospermic men and 3% - 10% of oligozoospermic men with normal karyotype [6,15]. Y chromosomal microdeletions are considered as the most frequent structural chromosomal abnormality associated with failure in sperm production [54].

### Y- Chromosome

Y-chromosome is the study of interest for male factor infertility as it contains many genes that are critical for spermatogenesis and development of male gonads. The human Y-chromosome is the smallest chromosome and consists of short (Yp) and a long (Yq) arm [55,56]. The pseudo autosomal region of Y chromosome (PAR1 and PAR2) located on both telomeric ends, which pairs with the X-chromosome during meiosis and show an autosomal pattern of inheritance [57, 56]. Euchromatin region consist of Yp i.e. Yp11 and the proximal part of Yq correspond to Yq11 and a heterochromatic distal region Yq12 (Fig. 1). The region other than PAR that does not recombine is called as non-recombining region of the Y-chromosome (NRY). After Tiepolo and Zuffardi (1976), Vogt *et al.* (1996) analysis showed three different phases of spermatogenic disruption corresponding to deletion in three different regions of AZFa, AZFb and AZFc at Yq11 [58,59]. The AZFa loci is located at the proximal portion of the deletion interval 5, the AZFb region spans from the distal portion of the deletion interval 5 to proximal end of deletion interval 6 [60] and the AZFc region is located at the distal part of deletion interval 6 [55]. Apart from this a fourth loci designated as AZFd is suggested to exist between AZFb and AZFc [61]. The initial Vergnaud interval map Vergnaud *et al.* 1986 [62] divided the Y chromosome into seven intervals (Fig. 2) includes short arm and centromere contain intervals 1-4, euchromatic part of Yq is represented by intervals 5 and 6, the heterochromatic region is represented as interval 7. Deletion interval 5 corresponds approximately to Yq11.21 to middle part of Yq11.22, and deletion interval 6 corresponds to the middle part of Yq11.22 to Yq11.23. On this basis, Vollrath *et al.* (1992) [63] further divided the seven-interval map in 43 subintervals, and this is the most frequently used map.



**Fig. 1**

**Fig. 1.** Representation of cytogenetic partitions of Y chromosome and showing pseudo-autosomal region- PAR1 and PAR2 [59]

**Fig. 2**

**Fig. 2.** Seven interval map of Human Y chromosome and AZF regions- AZFa, AZFb and AZFc [59]

### AZFa

AZFa region is the smallest portion of the AZF located at the proximal portion of deletion interval 5 and molecular length is ~800 kb [64]. AZFa is having low deletion frequency and characterized by non-repetitive structure [65]. AZFa contain *USP9Y*, *DBY* and *UTY* genes which shows high homology to  $\Delta Sx^b$  interval present in mouse [66]. However, only two genes *USP9Y* and *DBY* are involved in spermatogenesis [66,67]. Ubiquitin-specific protease 9, Y chromosome (*USP9Y*) was the first functional gene identified in the AZFa by Brown *et. al* in 1998 [68]. Dead box on the Y (*DBY*) is the major AZFa candidate gene and involved in the development of premeiotic germ cells [69]. *DBY* gene produce two transcript, one is long transcript and another is short transcript expressed only in testis [66]. *DBY* gene has DEAD (Asp-Glu-Ala-Asp) box at the sequence level which encodes for a protein expressed only in testis tissue [70].

**Mechanism of deletion:** The two identical retroviral sequence of HERV15 located in proximal Yq11 (interval D3 and D6) show intrachromosomal recombination [71].



**Genotype-phenotype correlation:** When there is deletion in AZFa region, Sertoli cell only (SCO) syndrome phenotype is observed in which either no germ cells are visible or less number of germ cells are existing within seminiferous tubules [59]. Complete deletion in AZFa region where both the genes are deleted causes SCO syndrome and bilateral small-sized testes [69,71,72].

#### AZFb

AZFb region is located in the distal portion of interval 5 and the proximal portion of interval 6 and it spans around 6 Mb [73]. In AZFb four genes *EIF1AY*, *PRY*, *TTY2* and *RBMY* have been mapped and are testis specific which play important role in spermatogenesis [74]. *RBMY* was the first identified as AZFb candidate gene by Ma *et al.* in 1993 [75] and is profoundly studied. RNA binding motif on Y (*RBMY*) is found in multiple copies and most of them are pseudogenes [76]. There are 6 families of *RBMY* genes which make an approximate total of 30 *RBMY* genes on both the arm of Y chromosome but only *RBMY1* gene was actively transcribed and encode functional protein [75,77]. *RBMY* encodes four types of testis-specific RNA-binding proteins that are important in mRNA processing, transport and splicing [78].

**Mechanism of deletion:** Deletion of AZFb interval occur mainly by homologous recombination between P5 and P1 proximal palindromes, called P5/proximal-P1 deletion. This deletion incorporates loss of 1.5 Mb AZFc interval including 2 copies of *DAZ* gene [73,79].

**Genotype-phenotype correlation:** It is usually observed that when there is AZFb deletion commence meiotic arrest of spermatogenesis at primary spermatocyte stage [65]. Lager or complete deletion in AZFb region causes azoospermia and partial deletion causes mild to severe oligozoospermia [80].

#### AZFc

Deletion in AZFc region denotes the most frequent type of deletion pattern observed in azoospermic and severe oligozoospermic patients. *PRY2*, *BPY2*, *DAZ* and *CDY1* are four protein coding gene families mapped to AZFc interval [81]. AZFc region is located at distal end of interval 6 [55] and spans over 3.5 Mb [82]. Deletion in Azoospermia (*DAZ*) is important candidate gene family in AZFc region reported by Reijo *et al.* in 1995 [83], which was found to be deleted in 12-15% of a cohort of azoospermic men [84] and share significant homology to male infertility gene in *Drosophila boule* [85]. *DAZ* is multicopy (4 copies) gene family and are testis-specific present nearly in all animals

which encodes a RNA binding protein, localizes in the innermost layer of male germ cell epithelium and in the tails of spermatozoa [84,86,87]. Yamada *et al.* in 2010 [88] reported that patients with AZFc deletion showed increased apoptosis of germ cells.

**Mechanism of deletion:** Homologous recombination gives rise to partial AZFc deletions that is b1/b3, b2/b3, b2/b4 and gr/gr [81,89].

**Genotype-phenotype correlation:** Patients having AZFc deletions associated with range of phenotypical features, which ranges from azoospermia to mild/severe oligozoospermia. Partial deletion in AZFc region involve *DAZ* genes have been reported to cause hypospermatogenesis.

#### AZFd

AZFd region is present in between AZFb and AZFc and mainly screened by 4 STS markers namely sY133, sY145 sY152 and sY153. Existence of AZFd region received support as well as disapproval when screened in AZF region. The most deletion in AZFd region is the STS marker sY153 [80].

**Genotype-phenotype correlation:** Patients with microdeletion restricted to AZFd may have mild or even normal sperm count but associated with abnormal sperm morphology [61].

#### Screening of Y chromosome microdeletion by Sequence tagged site polymerase chain reaction

According to EAA/EMQN microdeletions in the general population is about 1 in 4000 but in infertile men the frequency of microdeletion is significantly increasing. The STS PCR technique is considered to be the standard method for routine laboratory diagnosis of Y chromosomal deletion offered to all men with severe oligozoospermia and azoospermia. Since karyotyping and southern blotting are labours process, time consuming, costly and complex techniques, STS PCR is a successful tool to be performed in laboratories which is a simple, reliable, reproducible, minimum time consuming, less costly, sensitive and automated technique [90]. Screening of only one non-polymorphic STS locus in AZF region of Y-chromosome is sufficient to determine the STS deletion presence or absence in AZFa, AZFb and AZFc but using two STS loci in each AZF region gives diagnostic accuracy [91]. According to the European Academy of Andrology (EAA) and the European Molecular Genetics Quality Network (EMQN) guidelines for molecular diagnosis of Y chromosomal microdeletions to reconfirm the presence of the microdeletions in all deleted samples, six pairs of STS primer pairs were used for the AZFa (sY84 and sY86) AZFb (sY127 and sY134) and AZFc (sY254 and sY255) microdeletion analysis

[12,91,92]. The current study of primer designing and standardization of the PCR condition needed for an accurate diagnosis. For the accurate diagnosis of microdeletions in Y- chromosome requires careful primer designing and standardization of PCR conditions. Moreover, appropriate controls including positive (fertile male) and negative (fertile female) control are of chief importance. Molecular genetics research opened new paths to the management, analysis for Yq microdeletion, diagnosis and therapy for male factor infertility.

### CONCLUSION:

Treating male with infertility problems specially azoospermia and sever oligozoospermia patients is a big challenge. To streamline the treatment, it is necessary to diagnose the etiology of infertile male. Deletion of the AZF region (AZFa, AZFb and AZFc) region are associated with abnormal spermatogenesis and these deletion have prognostic value. Identification and characterization of DAZ dysfunction through molecular diagnostic technique provide useful information for its further application to screen infertile male population. Because of worldwide higher incidence of Y-chromosome microdeletions among infertile patients, genetic screening may be advised to infertile patients before they undergo ART treatment. Although, ICSI overcome the natural barriers but infertility is a natural barrier to stop the transmission of undesirable genes to next generation.

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### Conflict of interest

No conflict of interest.

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**Table 1: Y chromosome microdeletions and chromosomal analysis in infertile patients worldwide from 2013 to 2015.**

Authors (Year)	Country	No. of Samples/patients	No. of STS markers, gene and regions	Findings					Chromosomal aberration
				Y-chromosome microdeletions					
				AZFa	AZFb	AZFc	Other	Total	
Ambulkar <i>et al.</i> 2015 [19]	India	Idiopathic non-obstructive infertile men= 160 Normal healthy fertile control= 50	STS: 12 Regions: AZFa, AZFb and AZFc Internal control: SRY	2.02% (3/148)	3.37% (5/148)	6.08% (9/148)	AZFbc= 1.35% (2/148)	19/148 (12.8%)	12/160 (7.5%)
Masoudi <i>et al.</i> 2015 [20]	Iran	Non-obstructive Azoospermic patients= 50 Severe Oligospermic patients= 10	STS: 7 Regions: AZFa, AZFb and AZFc Internal control: SRY	0%	0%	8.3%	ND	8.3% (4% in Azoospermic cases and 30% in Oligospermic patients)	ND
Kdous <i>et al.</i> 2015 [21]	Tunisia	Azoospermic patients= 54, Severe oligospermic patients= 30 and controls= 52	STS: 6 Regions: AZFa, AZFb and AZFc	0%	1.19% (1/84)	7.14% (6/84)	AZFbc= 1.19% (1/84)	8/84 (9.5%) [Azoospermic group 6/54 (11.1%) and Severe oligozoospermic group 2/30 (6.7%)]	Total 7/84 (8.3%) [Azoospermic patients 6/54 (11.1%) and Severe oligozoospermic 1/30 (3.3%)]
Naasse <i>et al.</i> 2015 [22]	Morocco	Azoospermic patients= 444 and Oligozoospermic patients= 129	STS: 6 Regions: AZFa, AZFb and AZFc Internal control: SRY	0%	0%	14.12% (12/85)	AZFbc= 4.70% (4/85)	16/85 (18.82%)	Total 60/573 (10.47%) [Azoospermia 58/444 (13.06%) and Severe oligospermia 2/129 (1.55%)]

Authors (Year)	Country	No. of Samples/patients	No. of STS markers, gene and regions	Findings					Chromosomal aberration
				Y-chromosome microdeletions					
				AZFa	AZFb	AZFc	Other	Total	
Bashi <i>et al.</i> 2015 [23]	Iran	Azoospermic men= 70, Oligospermic men= 30 and Fertile men= 100	<b>STS:</b> 4 <b>Regions:</b> AZFa, AZFb and AZFc <b>Internal control:</b> SRY	0%	1% (1/100)	5% (5/100)	AZFb= 1% (1/100)	7% (7/100) Also, Partial deletions AZFc in infertile group (gr/gr)= 9% (9/100), AZFc deletions (gr/gr) in the control group= 1% (1/100), b2/b3 deletions in five azoospermic subjects= 5% (5/100) and partial AZFc deletions (b2/b3) in the control group= 2% (2/100)	ND
Sathyanarayana and Malini 2015 [24]	India	Married individuals with proven fertility= 104 and Unmarried with unknown fertility status= 96	<b>STS:</b> 5 <b>Regions:</b> AZFc	ND	ND	0.05% (1/200)	ND	0.05% (1/200)	ND
Hammami <i>et al.</i> 2015 [25]	Tunisia	Infertile patients with Idiopathic Non-obstructive Azoospermia= 401	<b>STS:</b> 6 <b>Region:</b> AZFa, AZFb and AZFc	0%	0%	2.22% (2/90)	ND	2.22% (2/90)	12.22% (49/401)
Bernasovská <i>et al.</i> 2014 [26]	Slovakia	Azoospermic men= 227, Healthy women= 50 and Healthy men= 50	<b>STS:</b> 9 <b>Region:</b> AZFa, AZFb and AZFc	0.88% (2/227)	1.32% (3/227)	3.52% (8/227)	ND	5.73% (13/227)	ND
Elsaid <i>et al.</i> 2014 [27]	Sudan	Infertile men= 32	<b>STS:</b> 6 <b>Region:</b> AZFb and AZFc <b>Internal control:</b> SRY	-	12.5% (4/32)	18.75 (6/32)	AZFbc= 6.25% (2/32)	37.5% (12/32)	ND
Elfateh <i>et al.</i> 2014 [28]	China (Northeast China)	Azoospermic patients= 720, Oligozoospermic patients= 330 and Fertile men= 100	<b>STS:</b> 9 <b>Regions:</b> AZFa, AZFb and AZFc <b>Internal control:</b> SRY and ZFY	0.286% (3/1050)	1.714% (18/1050)	9.714% (102/1050)	AZFbc= 1.238% (13/1050)	12.95% (136/1050) [Azoospermic men 14.03% (101/720), and Oligospermic men 10.60% (35/330)]	19.43% (204/1050)
Khabor <i>et al.</i> 2014 [29]	Jordan	Infertile males= 100 (Azoospermia= 36 and Oligozoospermia= 64)	<b>STS:</b> 16 <b>Regions:</b> AZFa, AZFb and AZFc <b>Internal control:</b> SRY and ZFY	0%	0%	2% (2/100) [5.55% (2/36) in Azoospermic men]	AZFbc= 1% (1/100) [2.77% (1/36) in Azoospermic men]	3% [8.3% (3/36) in Azoospermic men and no deletion in Oligospermic men]	-

Authors (Year)	Country	No. of Samples/patients	No. of STS markers, gene and regions	Findings					Chromosomal aberration
				Y-chromosome microdeletions					
				AZFa	AZFb	AZFc	Other	Total	
Ocak <i>et al.</i> 2014 [30]	Turkey	Infertile patients= 500	<b>STS:</b> 7 <b>Regions:</b> AZFa, AZFb, AZFc and AZFd	0.2% (1/500)	0.4% (2/500)	4.2% (21/500)	AZFbc= 0.4% (2/500), AZFd= 0.2% (1/500) and AZFabc= 0.2% (1/500)	5.6% (28/500)	12% (60/500)
Qumsiyeh <i>et al.</i> 2014 [31]	Palestine	Infertile patients= 56 (Azoospermic men= 37 and Oligozoospermic men= 19)	<b>STS:</b> 6 <b>Regions:</b> AZFa, AZFb and AZFc <b>Internal control:</b> SRY and ZFY	0%	0%	0%	0%	None of the subjects was positive for deletions of the AZF regions tested.	25% (14/56) 11 men had 47,XXY, 1 had 48,XXXY, one was mosaic 46,XY/47,XX, and one mosaic 45,X/46,XY
Al-Achkar <i>et al.</i> 2013 [32]	Syria	Azoospermic patients= 97, Oligospermic patients= 49, Severe oligospermic patients= 16 and Fertile men= 100	<b>STS:</b> 28 <b>Regions:</b> AZFa, AZFb and AZFc <b>Internal control:</b> SRY and ZFX/ZFY	3.7% (6/162)	1.85% (3/162)	9.88% (16/162)	AZFd = 1.85% (3/162), AZFb = 1.85% (3/162), AZFac = 2.47% (4/162), AZFad = 0.62% (1/162), AZFbc = 4.32% (7/162), AZFbd = 0.62% (1/162), AZFabc = 0.62% (1/162) and AZFbcd = 0.62% (1/162)	28.4% (46/162)	12.34% (20/162)
Choi <i>et al.</i> 2013 [33]	Korea	Non-obstructive azoospermic (NOA) men = 213 and Oligoasthenoteratozoospermic (OATS) men= 76	<b>Regions:</b> AZFbc and AZFc	ND	ND	28.02% (81/289)	AZFbc = 10.03% (29)	38.06% (101/289)	ND
Siddiqui <i>et al.</i> 2013 [34]	Pakistan	Infertile men= 113 (Azoospermic men= 54, Severe Oligospermic men= 35 and Moderate oligospermic men= 24) and Fertile men= 50	<b>STS:</b> 10 <b>Regions:</b> AZFa, AZFb and AZFc	0%	0%	3.54% (4/113)	ND	3.54% (4/113) [Azoospermic men 5.5% (3/54) and Severe oligospermic men 2.86% (1/35)]	ND



Authors (Year)	Country	No. of Samples/patients	No. of STS markers, gene and regions	Findings					Chromosomal aberration
				Y-chromosome microdeletions					
				AZFa	AZFb	AZFc	Other	Total	
Saeed <i>et al.</i> 2013 [35]	Egypt	Idiopathic infertile men= 74	<b>STS:</b> 9 <b>Regions:</b> AZFa, AZFb and AZFc <b>Internal control:</b> SRY	1.35% (1/74)	21.63% (16/74)	16.21% (11/74)	2.7% (2/74) of AZFb, 1.35% (1/74) of AZFac, 28.37% (21/74) of AZFbc and 5.4% (4/74) of AZFabc	75.67% (56/74)	ND
Suganthi <i>et al.</i> 2013 [36]	India (South India)	Infertile men= 50 (Non-obstructive azoospermic men= 30, Severe oligozoospermic men= 20) and Normozoospermic fertile men= 25	<b>STS:</b> 15 <b>Regions:</b> AZFa, AZFb and AZFc	11.11 %	11.11 %	33.33 %	AZF a+c= 5.56% AZF a+b= 11.11% AZF b+c= 16.67% AZF a+b+c= 11.11%	36% (18/50) [AZFc (66.67%) followed by AZFb (50%) and AZFa (38.88%)]	ND
Zhang <i>et al.</i> 2013 [37]	China (Northeast China)	Infertile male patients= 4952, Healthy men and women= 60	<b>STS:</b> 9 <b>Regions:</b> AZFa, AZFb, AZFc and AZFd <b>Internal control:</b> ZFX/ZFY	0%	0%	0%	0%	None of the patient showed Y chromosome AZF microdeletions	1.62% (80/4952) patients with 47, XXY. (77 was azoospermic and 3 oligozoospermic men)

ND= Not defined