ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

Y-CHROMOSOME MICRODELETION AND MALE-INFERTILITY

K. Ranjith Babu*[1,2], Milind V. Bhutkar[3], Deepti Shastri[4], E. Manivannan[5]

[1]*Ph.D. Scholar, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamilnadu, India*

[2]*Department of Physiology, Dr.Patnam Mahender Reddy Institute of Medical Sciences, Chevella, Telangana, India*

[3]*Department of Physiology, VMKV Medical College, Salem, Tamilnadu, India*

[4]*Department of Anatomy, VMKV Medical College, Salem, Tamilnadu, India*

[5]*Department of Pharmacology, VMKV Medical College, Salem, Tamilnadu, India*

**Corresponding author: drranjithbabu@gmail.com*

ABSTRACT

Infertility is a multifactorial condition prevalent across the globe and a draws attention of whole world. Infertility is a concern as it may be due to idiopathic and may be due to congenital or acquired. Infertility is a condition in couple of young age which can be defined as failure to achieve pregnancy even after 12 months or more of regular unprotected sexual intercourse. A systematic search for the literature published was conducted in the MEDLINE-Pubmed database. The inclusion filters were 'Y chromosome deletions and male infertility'. Among the search results, the titles and abstracts of all the articles were screened for eligibility and relevance of the topic are selected as per the inclusion and exclusion criteria. After analyzing the above article we can say that Y chromosome has more chances of microdeletions which may be due to presence of palindrome structures with a more chances of homologous recombination among ampliconic sequences. It is also found that the prevalence or occurrence of Y-chromosome microdeletions in male infertile patients is varied throughout the world. Y-chromosome occurrence varied to a very high 75.68% to a low value of 0%.We can suggest that during the treatment of any infertility case, subsequent testing for any Y-chromosome microdeltions has to be done routinely before proceeding for any ART as it may result in carrying the same microdeletion to the next generation.

Keywords: AZFa, AZFb, AZFc, Male infertility, Y-chromosome Microdeletion

1. INTRODUCTION

Infertility is a multifactorial condition prevalent across the globe and a draws attention of whole world. Infertility is a concern as it may be due to idiopathic and may be due to congenital or acquired. Infertility is a condition in couple of young age which can be defined as failure to achieve pregnancy even after 12 months or more of regular unprotected sexual intercourse. Infertility is the inability of a sexually activity, non-contracepting couple to achieve pregnancy in one year [1]. Throughout the world, research is focused on infertility keeping in view the pain and agony of the childless couples across the globe. Further, the genetic causes of the Infertility can only be minimized by better understanding the type and probable cause of the change in the genetic structure of the genes leading to condition of Infertility. Infertility affects up to 15% of reproductive-aged couples worldwide. According to World Health Organization estimate the overall prevalence of primary infertility in India is between 3.9 to 16.8%.In Indian states also, the prevalence of infertility varies from state to state such as 3.7 per cent in Uttar Pradesh, Himachal Pradesh and Maharashtra, to 5 per cent in Andhra Pradesh, and 15 per cent in Kashmir and prevalence varies in same region across tribes and caste [2].

Genetic abnormalities or deletions are often associated in infertile men associated with abnormalities of semen like oligozoospermia and azoospermia. Genetic factors involved in male infertility manifest as chromosomal disorders, mitochondrial DNA (mt DNA) mutations, monogenic disorders, multifactorial disorders and endocrine disorders of genetic origin. Some abnormalities associated with infertility are inherited, like reciprocal and Robertsonian translocations and CFTR mutations. Of all the genetic factors, the study of Y chromosome microdeletions is particularly important because of the potential for transmission of genetic

abnormalities to the offspring, as these techniques bypass the physiological mechanisms related to fertilization. Quite recently, sperm mitochondrial mutations have been gaining much attention. The first insight into the correlation between the Y chromosomal microdeletion and male infertility came from the studies of Tiepolo and Zuffardi in 1976 [3]. Later on with the development of STS and YAC based mapping, several interstitial microdeletions which are present on the long arm of Y chromosome (Yq11) were identified [4-5].

The human Y-chromosome has a short (Yp) and a long (Yq) arm. Y-chromosomal microdeletions(YCM) are the absence of DNA segments or genes from the functionally active part.

2. MATERIAL AND METHODS

A systematic search for the literature published was conducted in the MEDLINE-Pubmed database. The inclusion filters were 'Y chromosome deletions and male infertility'. Among the search results, the titles and abstracts of all the articles were screened for eligibility and relevance of the topic. Articles with Original-interventional, Original-Research, Case-control, Cross-sectional and Observational prospective and retrospective studies related to Y chromosome deletion in male-infertility are considered as the inclusion criteria of the study. Only articles published in english language are included in the present study.

Each article satisfying the inclusion criteria is thoroughly studied and the following information is collected and tabulated in MS-Office Excel software under following headings: Title of the Article, Author(s), Name of the Journal, Year of publication, location of study, sample size and control size (if any), study design, number of subjects with Y chromosome microdeletions, percentage of appearance of Y chromosome microdeletions, any other significant findings. The articles which are excluded are Letters to the Editor, Prefaces, Brief Communication, Corrections/Erratum, Reviews, Editorials and Monographs.

The institutional ethical clearance was not required as this is a Review of the Literature of the Articles which are published on Y chromosome microdeletions in male infertile subjects.

3. RESULTS

As per the Inclusion criteria during searching of the articles, only those articles which are concerned with Y chromosome microdeletions in male infertiles are only downloaded. A total of 72 articles have been obtained which are relevant to the study topic. After careful study, out of these 72 articles, 27 articles have been excluded as they do not meet the inclusion criteria of the study. Rests of the 45 articles were relevant to the study and are as per the inclusion criteria. These 45 articles are carefully studied and the data pertaining to the information is tabulated for further comparative study and analysis as mentioned earlier (Table 1).

Hesham Saeed et al designed a group of gene specific PCR primers for nine genes in the Y-chromosome from the published STS map. These primers were used to screen 74 adult male Egyptian patients with idiopathic infertility with age ranged from 24-36 years and the duration of infertility in all of them ranged from 6 months up to 10 years. Results showed that, by applying simple and multiplexing PCR for nine genes on Y-chromosome, fifty six patients were found to carry Y chromosome microdeletions (75.67%) and the highest frequency was that of the DAZ gene which account for twenty seven patients (36.49%) [6].

Sandra E Kleiman et al made a retrospective study of evaluating DNA of 1,260 infertile men for AZF microdeletions. The DNA of 657 of them with undetected microdeletions was analyzed for partial AZFa deletion in the USP9Y and DDX3Y genes using sequence-tagged sites beyond EAA/EMQN recommendations. Two men had complete AZFa deletion (a frequency of 0.28% among nonobstructive azoospermic men). None had partial AZFa deletions [7].

Ali Mohammad Malekasgar et al have observed 26/50 cases (52%) showed deletion of at least one of the STS Marker. Totally 41 microdeletions was observed. A total of 17 cases (34%) had deletion in one STS. Four oligospermia cases (8%) had deletion in 2 STS site. Three azoospermia cases (6%) had again deletion in 2 STS site, but in different STSs. One case had three deletions in three STS site and finally one individual had seven deletions in AZF locus. The overall frequency of Y chromosome microdeletions observed in the present study was found to be 26/50 (52%) [8].

Mostafa AkbarzadehKhiavi et al selected a total of 94 infertile males with nonobstructive azoospermic and aged 24 to 53 years for their study. Among the 94 infertile men, a total of 48 cases (48/94, 51.06%, $P< 0.01$) were found to have deletions in the regions of AZFb, AZFc and AZFd. Of the 48 azoospermic subjects harbouring Y chromosome microdeletions, twelve had deletions in AZFb, twenty in AZFc, six in AZFb+c, two in

AZFb+c+SRY, twoin AZFc+d, two in A ZFb+d, two in AZFb+ SRY and two in AZFb+c+d regions [9].

Don Kyung Choi et al retrospectively reviewed clinical data from 213 patients with nonobstructive azoospermia (NOA) and 76 patients with oligoasthenoteratozoo-spermia (OATS) who were tested for Y chromosome microdeletion from March2004 to June 2011.Of the 289 patients, 110 patients presented with Y chromosome microdeletion and 179 patients presented with no microdeletion. After subdividing the patients with Y chromosome microdeletion, 29 had azoospermia factor (AZF)b-c microdeletion and 81 had AZFc microdeletion [10].

C. Krausz et al in a blind study had screened 131 infertile males (46 idiopathic and85 nonidiopathic) for Y chromosome microdeletions. Nineteen percent of idiopathic males,with an apparently normal 46,XY chromosome complement had microdeletions of either theAZFa, AZFb, or AZFcregion. Significantly, ahigh frequency of microdeletions (7%) was found in patients withknown causes of infertility and a 46,XY chromosome complement.These included deletions of the AZFb and AZFc regions, with nosignificant difference in the location or extent of the deletion compared with the former group

A Ferlin et al using a PCR based screening analyzed Yq microdeletions in 180 infertile patients affected by idiopathic Sertoli cell-only syndrome and different degrees of hypospermatogenesis, compared with 50 patients with known causes of testicular alteration, 30 with azoospermia, 100 normal fertile men. In idiopathic severe testiculopathies, a high prevalence of microdeletions (34.5% and 24.7% respectively) was found [12].

Barbara Arredi et al made a study to assess whether some Y-chromosome haplogroups are predisposing to, or protecting against, azoospermia factor c (AZFc; b2/b4) deletions, 31 north Italian patients carrying the AZFc b2/b4 microdeletion were characterised for 8 Y-chromosome haplogroups, and compared with the haplogroup frequency shown by a north Italian population without the microdeletion (n = 93).A significant difference was observed between the two populations, patients with microdeletions showing a higher frequency of the E haplogroup (29.3% vs 9.7%, p,0.01) [13].

Poongothai J et al included a total of 287 men, 147 infertile men and 140 normozoospermic fertile controls for the study. Screening 72 semen samples with the STS markers specific to AZF (a,b,c) regions showed Y chromosome microdeletions in 19 (12.9%) individuals. No deletion was observed in all the three AZF regions by screening 45 blood and 30 paired samples. None of the control men showed deletion for the 28 STS markers, which were used for the primary screening of the deletion of AZF a,b,c regions [14].

Dr Manuela Simoni screened a total of 3179 patients for Y-chromosome microdeletions and 821 patients for partial AZFc deletions. Thirtynine Y-chromosomal microdeletions were found (2.4% of men with $<1 \times 106$/ml spermatozoa): two AZFa, twoAZFb, oneAZFbc, one partial AZFb, one partial AZFb+c and 32 AZFc (b2/b4). Partial AZFc deletions were found in 45 patients (5.5%), mostly gr/gr deletions (n = 28) [15].

In their research study by Han-Sun Chiang et al, a total of 334 consecutive men with azoospermia (218 patients) and severe oligoasthenospermia (116 patients) were screened. In the 334 patients, the occurrence of genetic defects was 22.5 %, including 53 (15.9 %) with chromosome disorder and 30 (9.0%) with gene deletion on the Y chromosome. There were 8 cases (6 azoospermia and 2 severe oligoasthenospermia) with both chromosome disorder and gene deletion on the Y chromosome. Patients with azoospermia had a higher incidence of chromosome disorder (20.6%) than patients with severe oligoasthenospermia, however, in this study; patients with severe oligoasthenospermia had a higher incidence of Y gene deletion (10.3%) than those with azoospermia (8.3%). In routine screening for Y chromosome microdeletion, they found there are thirty cases (18 azoospermic and 12 severe oligoasthenospermic) out of 334 infertile patients had deletion of the variable portions of the Yq arm. In this study, the deletion area on Y chromosome was classified into 2 groups in correspondence with the 2 AZF regions and the severity of spermatogenic deficit. Group 1 (19 cases) had one case with microdeletion distal to the AZFc region on the long arm of Y chromosome and the other 18 cases had their Y chromosome gene in AZFc region (between sY153 and sY277). Group 2 (11 cases) include 2 cases with deletions in AZFb, and the other 8 had 6 kinds of deletions with variable length of region located from AZFc to AZFb [16].

Ramaswamy Suganthi et al performed PCR based Y chromosomal microdeletion screening analysis in 75 men including 30 non- obstructive azoospermic men, 20 severe oligozoospermic, and 25 normozoospermic fertile men (controls) using 15 known STS primer pairs mapped

within the AZF locus. Deletion frequency was estimated after successful PCR amplification. The estimation for overall deletion frequency was 36%. Among these 12 (40%) were azoospermic and 6 (30%) were oligozoospermic. No microdeletions were observed in normozoospermic fertile men [17].

ArdeshirBahmanimehr et al made a case-control study of 97 oligozoospermic or non-obstructive azoospermic (NOA) infertile men, who had undergone ART, as the case group and 100 fertile men as the control group. DNA samples were extracted from blood samples taken from all 197 participants and YCDs were identified by multiplex polymerase chain reaction (PCR) of eight known sequence-tagged sites. No YCD was detected in the control group. However, 20 out of 97 (20.6%) infertile men had a YCD. AZFc, AZFbc and AZFabc deletions were detected in 15 (75%), four (20%) and one (5%) YCD-positive patients [18].

X G Liu et al studied 166 infertile males and 50 fertile males using multiplex polymerase chain reactions amplification and gel electrophoresis. The results demonstrated that 28 individuals had varying degrees of microdeletion in the AZF region (16.90%); 12 out of the 76 males with azoospermia and 16 out of the 90 males with oligospermia had AZF microdeletion. AZF microdeletion was not observed in any of the healthy controls. In addition, 53.60% of the AZF microdeletions occurred in the AZFc region [19].

YassineNaasse et al referred a total of 573 Moroccan infertile men (444 azoospermic and 129 oligozoospermic men) for cytogenetic analysis. Molecular analysis was performed to detect Y chromosome microdeletions in 85 patients. Among these patients, twelve had a deletion of AZFc (14.12 %), four cases had a deletion of AZFbc, and 69 cases had an intact Y chromosome (81.18 %). No patient with a deletion of AZFa, AZFb or AZFabcwas observed [20].

G. Rekha et al evaluated the patterns of Y-chromosome microdeletion in male infertility cases (N=147) attending the infertility clinic. PCR based Y chromosome microdeletion analysis revealed nearly 14.28% (21/147) deletions in the infertile men with idiopathic infertility, of which 5.4% deletion among Azoospermic men, 2.72% among severe Oligospermic men, 4.08% among Oligospermic men and 2.04% among Asthenozoopermic, Oligoasthenoteratoazoospermic, Astheno-teratozoospermic men [21].

In a study by Ting Liu et al, 1274 patients with azoospermia and oligozoospermia were recruited in southwest of China and screening for Y chromosome microdeletions in AZF regions by multiplex polymerase chain reaction. The incidence of AZF microdeletions in southwest of China is 12.87%, which is higher than the national average. Further investigations unveiled that azoospermia factor c (AZFc) is the most frequent type of all the AZF microdeletions. Additionally, the number and also the quality of sperm in patients with AZFc microdeletion is decreasing with the age [22].

A study was carried by ArzuVicdan et al out in 208 infertile and 20 fertile men. Results of 208 patients, 119 had non-obstructive azoospermia and 89 had severe oligoasthenoteratozoospermia (OAT). Seventeen out of 119 (14.3%) azoospermic patients and two out of 89 (2.2%) patients with OAT had Y chromosome microdeletions. In total, 19 cases with deletions were detected in 208 infertile men, with a frequency of 9.1%. The AZFc locus, mainly DAZ gene cluster was the most frequently deleted region. Five other cases with azoospermia (4.2%) and two cases with OAT (2.2%) had a chromosomal abnormality, with a total number of seven (3.4%). Including Y chromosome deletions and structural chromosome abnormalities, the rate of genetic abnormalities was 12.5% (26/208) in the patients. On the other hand, 20 men with proven fertility and fathers of five cases with microdeletions were genetically normal [23].

In their study by Walid Al-Achkar et al, karyotyping was performed for the 100 controls and 162 infertile men with azoospermia (n=97), oligozoospermia (n=49) and severe oligozoospermia (n=16). No chromosome abnormalities were detected in the controls. Of the 162 (12.34%) infertile patients, 20 had chromosomal abnormalities, including 17 of the 97 (17.52%) patients with azoospermia and 3 of the 49 (6.12%) patients with oligozoospermia [24].

F.H. Khan et al studied population was composed of 25 men with moderate exposure to HCH (farmers). Found threemen with Yq deletion in AZFa and AZFc regions (5.55%) in exposed group. All subjects have normal semen quality except subject-F25 (Farmer) with40%sperm motility (asthenospermic) without anyYq deletion and Ex7 (exposed group) with 20% sperm motility (severe asthenospermic), showing deletion of sY95, sY1161, sY1191 and sY1206 while Ex3 with normal semen quality, showing deletion of sY1161. The subject Ex4 is suffering from idiopathic infertility, showing deletion of sY95. The findings of this study

indicated that the exposure of HCH may cause Yq deletions [25].

In a study by Saima Siddiqi et al, deletion analysis of the AZF a, b and c regions was carried out in 51 infertile males and 100 control males with known fertility. Data revealed AZFa deletion in 2% infertile azoospermic and oligospermic males, while the AZFb and AZFc deletions were found in 3.8 and 5.8% infertile males, respectively [26].

Shin Young Kim et al have reported Y microdeletions in 134 out of 1,226 inferile patients. One hundred seven of 765 (13.99%) non-obstructive azoospermic patients and 27 of 133 (20.30%) severe oligozoospermic patients had Y microdeletions. Among the 134 infertile men with Y microdeletions, the most frequent microdeletions were detected in the AZFc region, followed by AZFbc, AZFb, AZFa, AZFabc(Yq), Yp(SRY)+Yq, and partial AZFc regions [27].

Florina Raicu et al diagnosed three men with microdeletions of the long arm of the Y chromosome among the 30 patients, corresponding to a proportion of 10% [28].

Carolina Gonçalves et al made comparisons between the different types of Y-microdeletions (AZFa, AZFb, and AZFc) andtreatments, with detailed demographic, stimulation, embryological, clinical, and newborn (NB) outcomes. Of 125 patients with Y-microdeletions, 33 patients presented severe oligozoospermia (18 performed ICSI with ejaculated sperm) and 92 secretory azoospermia (65 went for TESE with 40 having successful sperm retrieval and performed ICSI). There were 51 TESE treatment cycles and 43 TESE-C treatment cycles, with a birth of 19 NB (2 in AZFa/TESE-C, 12 in AZFc/TESE, and 5 in AZFc/TESE-C). Of the 29 EJAC cycles, there was a birth of 8 NB (in AZFc). In TESE and EJAC cycles, there were no significant differences in embryological and clinical parameters. In TESE-C cycles, there was a significant lower oocyte maturity rate, embryo cleavage rate and mean number of embryos transferred in AZFb, and a higher mean number of oocytes and lower fertilization rate in AZFc [29].

Zakaria Mahran et al have studied 50 infertile severe oligozoospermic patients. In their study they have reported AZF microdeletions in 4 cases [30].

Raheleh Masoudi et al selected 81 infertile males with non-obstructive azoospermia or oligozoospermia. Multiplex PCR using several STS markers was carried out to detect the complete or partial microdeletions. The frequency of both complete and partial microdeletions in men with azoospermia or severe oligozoospermia was 7.4%. All microdeletions were observed in AZFc region. There was 1.25% complete microdeletions and after excluding complete microdeletions, detected 5% gr/gr and 1.25% b2/b3 microdeletions. In control group of fertile males, 4% gr/gr microdeletions was detected while there was no b2/b3 microdeletions [31].

J.M. Pina-Neto et al studied 165 infertile men whose infertility was attributable to testicular problems (60 were azoospermic, 100 were oligospermic and 5 were asthenospermic). Karyotyping revealed somatic anomalies in 16 subjects (16/165=9.6%). Of these 16, 12 were in the azoospermic group (12/60 = 20%) and 4 were in the oligospermic group (4/100=4%). The most common chromosomal anomaly was Klinefelter syndrome (10/165=6%). Microdeletions ofAZF genes were detected in 12 subjects (12/160=7.5%) [32].

Jon L Pryor et al studied 200 consecutive infertile men. Fourteen infertile men (7 percent) and four normal men (2 percent) had microdeletions of the Y chromosome. Nine of the infertile men had azoospermia or severe oligospermia, four had oligospermia, and one had normospermia [33].

Masashi Iijima et al in their study included 1030 male patients with infertility who were examined for Y chromosome microdeletion. Among the 1030 patients, 4, 4, 10, and 52 had AZFa, AZFb, AZFb+c, and AZFc deletions respectively. The sperm recovery rate (SRR) of microdissection testicular sperm extraction in patients with AZFc deletions was significantly higher than that in those without AZF deletions (60.0% vs 28.7%, P = 0.04). In patients with gr/gr deletion, SRR was 18.7%, which was lower than that in those without gr/gr deletion, but was not statistically significant [34].

Rama Devi Mittal et al studied prevalence of microdeletions on the Y chromosome in 79 infertile with azoospermia and oligozoospermia using Polymerase chain reaction (PCR) micro-deletion analysis. Seven sets of primers were used encompassing AZFa, AZFb andAZFc regions. Micro-deletions in five of the 79 cases (6.3%) showed deletions of at least one of the STS markers. Deletions were detected with known and unknown aetiology and at least in one of the infertile male with varicocele [35].

Sandeep Kumar Bansal et al analyzed the AZFc region of the Y-chromosome for complete (b2/b4) and distinct partial deletions (gr/gr, b1/b3, b2/b3) in 822 infertile and 225 proven fertile men. They observed complete

AZFc deletions in 0.97% and partial deletions in 6.20% of the cases [36].

Dwi Anita Suryandari et al used PCR method with five STS to locate deletion onthree different subregions (AZFa, AZFb, and AZFc) of azoospermic men and one STS to amplify SRY gen which act asan internal control. In their study, they detected two of 35 (5,7%) azoospermic men had microdeletion Yq. One had microdeletion on subregionAZFa (sY84) and AZFb (RBMY1) and the other one on subregionAZFc (sY254 and sY255) [37].

Ran Zhou et al in their study, performed multiplex ligation-dependent probe amplification (MLPA) analysis on 402 fertile healthy male controls and 423 idiopathic infertile SF patients (197 azoospermia and 226 oligozoospermia) in Han Chinese population. In total, twenty-four types of AZF-linked CNVs were identified in our study, including eleven novel CNVs (one deletion, seven duplications, and three complex CNVs). Further, the study revealed that AZFc-linked duplications and the instability of Y chromosome might be associated with spermatogenesis. Besides, the complex CNVs (b2/b3 deletion + DAZ1/2 duplication) were confirmed to increase genetic risks for SF in Han Chinese population [38].

Blanka Chylíková et al compared 107 males with pathological sperm evaluation resulting in nonobstructive infertility to 131 males with normal fecundity. Isolated Xcnv64 deletion in 3 patients and 14 controls, and Xcnv69 in 3 patients and 6 controls (1 and 1 patient vs.4 and 1 control for types A and B respectively). There was one control with combined Xcnv64 and Xcnv69 type B deletions,and one patient with combination of Xcnv64 and Xcnv69 type C deletions. In conclusion, association of X-chromosome microdeletions at Xq27.3 and Xq28 withmale infertility could not be confirmed nor excluded for Czech males [39].

Katya Kovacheva et al study was retrospective and involved a total of 142 infertile Bulgarian males (63 patients with azoospermia and 79 patients with severe oligozoospermia /sperm count < 5×106/ml). Chromosomal abnormalities were found in 16.8% of all investigated infertile men and the frequencies in patient subgroups with azoospermia and oligozoospermia were 20.7% (12/58) and 13.9% (11/79) respectively. The overall proportion of the two genetic factors was 30.2% in patients with azoospermia and 14% in men with oligozoospermia [40].

Fahimeh Asadi et al examined 1885 infertile men referred to Royan Institute with azoospermia/severe oligospermia for Y chromosome microdeletions. Among the 1885 infertile men, they determined 99 cases of Y chromosome microdeletions (5.2%). Among 99 cases, AZFc microdeletions were found in 70 cases (70.7%); AZFb microdeletions in 5 cases (5%); and AZFa microdeletions in only 3 cases (3%). AZFbc microdeletions were detected in 18 cases (18.1%) and AZFabc microdeletions in 3 cases (3%) [41].

Shailesh Pande et al have conducted PCR based Y microdeletion studies in 763 patients aged 21-47 years with suspicion of Y microdeletion. Microdeletions was observed 30 patients with a total deletion rate of 3.9% [42].

Ali Hellani et al have screened a total of 257 patients with idiopathic oligo- or azoospermia for Y chromosome microdeletions by 19 markers in AZF region. Ten (3.9%) patients had chromosomal rearrangements, six of them showed sex chromosome abnormalities and four patients had apparently balanced autosomal rearrangements. Eight of the remaining 247 patients (3.2%) with a normal karyotype and no known causes of impaired spermatogenesis had Y chromosome microdeletions. Among these, six patients had deletions in AZFc region, one case had a deletion inAZFb and another had both AZFa and AZFc deletions [43].

Yuan Pan et al found a total of 190 Y chromosome abnormality carriers of whom 35 had AZF microdeletions. These were most common in 46, X, Yqh patients, followed by 45,X/46,XY patients. Most microdeletions were detected in the AZFbþc region, including 48.57% of all AZF microdeletion cases. AZF partial deletions were also seen in these patients. Overall, AZF microdeletions were detected in 38.5% Y chromosome abnormality carriers, and most wereobserved in 46, X, Yqh individuals. Loss of SY152 was seen in all 35 patients, with SY254/SY255 detected in 34 of 35 patients [44].

S Venkatesh et al studied forty-eight couples with history of RSA and 20 fertile controls. One of 48 men (2%) showed 46, XY (1qh-) chromosomal complement. None of the cases including FC showed deletion in any of the 3 AZF loci on Y chromosome long arm [45].

Afsaneh Mojtabanezhad Shariatpanahi et al in their case control study; genomic DNA was extracted from 80 male samples including 40 non-obstructive infertile men, 20 males from couples with RPL and 20 fertile males as control. Only one subject was detected to have Y

chromosome mcrdeletions in SY254, SY157 and SY255 among the 40 men with non-obstructive infertility [46].

Sarah K. Girardi et al evaluated the frequency of Y chromosome deletions in 160 infertile men using a series of 36 sequence-tagged-sites, emphasizing intervals 5 and 6 of the long arm of the Y chromosome. Two distinct regions of Y chromosome deletions were detected, ~3.6 Mb and 1.4 Mb in length respectively. These deleted regions are present in AZFb and AZFc respectively. No deletions were detected in AZFa [47].

Table 1: Summary of articles published on Y Chromosomal microdeletions analysis

S. No.	Authors	Year of Publication	Number of subjects	Number of Y chromosome microdeletions	% of Y chromosome microdeletions
1	Hesham Saeed et al	2013	74	56	75.68
2	Sandra E. Kleiman et al	2012	1260	657	52.14
3	Ali Mohammad Malekasgar et al	2008	50	26	52.00
4	Mostafa AkbarzadehKhiavi et al	2013	94	48	51.06
5	Don Kyung Choi et al	2012	289	110	38.06
6	C. Krausz et al	1999	131	46	35.11
7	A.Ferlin et al	1999	180	62	34.44
8	Barbara Arredi et al	2006	93	31	33.33
9	Poongothai J. et al	2008	72	19	26.39
10	Manuela Simoni et al	2008	3179	821	25.83
11	Han-Sun Chiang et al	2004	334	83	24.85
12	RamaswamySuganthi et al	2012	75	18	24.00
13	ArdeshirBahmanimehr et al	2018	97	20	20.62
14	X.G. Liu et al	2016	166	28	16.87
15	YassineNaasse et al	2015	573	85	14.83
16	Dr. G. Rekha et al	2019	147	21	14.29
17	Ting Liu et al	2019	1274	164	12.87
18	ArzuVicdan et al	2004	208	26	12.50
19	Walid Al-Achkar et al	2012	162	20	12.35
20	F.H. Khan et al	2010	25	03	12.00
21	Saima Siddiqi et al	2009	51	6	11.76
22	Shin Young Kim et al	2017	1226	134	10.93
23	Florina Raicu et al	2003	30	03	10.00
24	Carolina Gonçalves et al	2017	1387	128	9.23
25	ZakariaMahran et al	2016	50	04	8.00
26	RahelehMasoudi et al	2016	81	06	7.41
27	J.M. Pina-Neto et al	2006	165	12	7.27
28	Jon L. Pryor et al	1997	200	14	7.00
29	Masashi Iijima et al	2019	1030	70	6.80
30	Rama Devi Mittal et al	2004	79	05	6.33
31	Sandeep Kumar Bansal et al	2016	822	51	6.20
32	Dwi Anita Suryandari et al	2006	35	02	5.71
33	Ran Zhou et al	2019	423	24	5.67
34	BlankaChylíková et al	2016	107	06	5.61
35	Katya Kovacheva et al	2018	109	6	5.50
36	FahimehAsadi et al	2017	1885	99	5.25
37	ShaileshPande et al	2018	763	30	3.93
38	Ali Hellani et al	2006	257	10	3.89
39	Yuan Pan et al	2017	5235	190	3.63
40	S. Venkatesh et al	2011	48	01	2.08
41	Afsaneh Mojtabanezhad Shariatpanahi et al	2018	80	01	1.25
42	Sarah K.Girardi et al	1997	160	02	1.25
43	Shalaka S Ramgir et al	2017	10	00	0.00
44	Ashraf J. Shaqalaih et al	2016	125	00	0.00
45	S Ghorbian et al	2012	100	00	0.00

Shalaka S Ramgir et al collected 10 azoospermic patient and 10 control men samples from the Sandhya hospital, Vellore. In this study, they mainly focused on AZFa region to analyze the frequency of microdeletions in Y chromosome using SY82 (264bp) and SY83 (275bp) STS markers. There was an absence of microdeletion in patient samples for SY82 and SY83 markers of AZFa region [48].

Ashraf J Shaqalaih et al studied 50 fertile males (controls) and 125 patients with primary idiopathic male infertility. No Y chromosomeclassical microdeletions could be detected in any of the 125 infertile men, suggesting that ethnicfactors, genetic background, and Y chromosome haplogroups are key factors in such deletions. On the otherhand, six gr/gr and one b1/b3 AZFc partial deletions were detected in the infertile population. The gr/gr deletionwas also noted in relatives of four of the six patients with this deletion, and in one of the fertile controls [49].

S Ghorbian et al included one hundred men from couples, experiencing three or more RPLs, and one hundred normal men from couples with at least one child and no history of miscarriages as control group. Genomic DNA was extracted from peripheral blood and tested for Y chromosome microdeletions in AZFa, AZFb and AZFc regions using two multiplex PCR. None of the men in the case and control groups had any microdeletions in the AZFa, AZFb and AZFc regions [50].

Upon analysis of the article, it is observed that the infertility is a condition which is prevalent globally. But, on analysis of the articles it is found that the prevalence or occurrence of Y-chromosome microdeletions in male infertile patients is varied throughout the world. Y-chromosome occurrence varied to a very high 75.68% as observed by Hesham Saeed et al and low to value of 0% as observed by Shalaka S Ramgir et al, Ashraf J. Shaqalaih et al and S Ghorbian et al. This suggests that a stardardisation of the procedure for study of Y-chromosome microdeletions has to be made. If all the authors have followed the same standardised procedures then their findings and results can be compared and a conclusion can be drawn. Along with stardardisation of the procedure, the concerned technicians or investigators also have to undergo relevant training.

4. CONCLUSION

Even though there are major advancements in the field of science & technology and Medicine, infertility is still prevalent and is a major public concern. Except for the 3 articles, the analysis has shown presence of Y-chromosome microdeletions in the male infertile patients. After analyzing the above article we can say that Y chromosome has more chances of microdeletions which may be due to presence of palindrome structures with a more chances of homologous recombination among ampliconic sequences. The consequence of the unrequired microdeletions is resulting in a condition of infertility. With this information, we can suggest that during the treatment of any infertility case, subsequent testing for any Y-chromosome microdeltions has to be done routinely before proceeding for any ART as it may result in carrying the same microdeletion to the next generation. Further studies including more number of subjects with inclusion of more genes may be done.

5. REFERENCES

1. Rowe Pj, ComhaireFh, Organization Wh, Hargreave Tb et al. Cambridge University Press. 2000.
2. National Health Portal-India.[Online] Available From: https://www.nhp.gov.in/Disease/Reproductive-System/Infertility [Accessed On 3rd February 2020].
3. Tiepolo L, Zuffardi O. *Hum Genet*, 1976; **34(2)**:119-124.
4. Foote S, Vollrath D, Hilton A, Page Dc. *Science*. 1992; **258(5079):**60-66.
5. Vollrath D, Foote S, Hilton A, Brown Lg et al.*Science*. 1992; **258(5079):**52-59.
6. Saeed H, Neamattallah H, Zaghloul T, Elmolla K. *Life Sci J*, 2013;**10(4):**1191-1199.
7. Sandra E Kleiman, Ronit Almog, Leah Yogev, Ron Hauser et al. *Fertility and Sterility*, 2012; **98(1):**43-47e.
8. Ali Mohammad Malekasgar, Hayat Mombaini. *J Hum ReprodSci*, 2008; **1(1):**1-9.
9. Mostafa Akbarzadeh Khiavi, Seyyed Ali Rahmani, Azam Safary, Hossein Nikzad et al. *Jokull Journal*, 2013; **63(10):**44-53.
10. Don Kyung Choi, In Hyuck Gong, JinHo Hwang, Jong Jin Ohet al.*Korean J Urol*, 2013; **54(2)**:111-116.
11. CKrausz, L Quintana-Murci, S Barbaux, J-P Siffroi et al. *The Journal of Clinical Endocrinology & Metabolism*, Oct 1999; **84(10):**3606-3612.
12. AFerlin, EMoro, AGarolla, CForesta. *Human Reproduction*, 1999; **14(7):**1710-1716.
13. BarbaraArredi, Alberto Ferlin, Elena Speltra, Chiara Bedin et al. *J Med Genet*, 2007; **44(3)**:205-208.

14. Sakthivel Jp, Swaminathan M. *Indian J Urol*, 2008; **24(4):**480-485.
15. Dr Manuela Simoni. *Reproductive Biomedicine Online*, 2008; **16(2):**289-303.
16. Han-Sun Chiang, Shauh-Der Yeh, Chien-Chih Wu, Boo-Chung Huang et al. *Asian J Androl*, Dec 2004; **6(4):**369-375.
17. Ramaswamy Suganthi, Vijesh V, Sanjay Jayachandran, Jahangir Ali et al. *Iran J Reprod Med*, 2013; **11(3):**219-226.
18. Bahmanimehr A, Zeighami S, Namavar Jahromi B, Anvar Z, Parsanezhad M et al. *Int J Fertil Steril.,* 2018; **12(2):**173-177.
19. XG Liu, HY Hu, YH Guo, YP Sun. *Genetics and Molecular Research*, 2016; **15(2):**1-8.
20. Yassine Naasse, Hicham Charoute, Brahim E Houate, Chadli Elbekkay et al. *BMC Urology*, 2015; **15:**95.
21. Rekha G, Rajitha V, Paramesh G. *Indian Journal of Applied Research*, 2019; **9(3):**66-68.
22. Ting Liu, Yu-Xin Song, Yong-Mei Jiang. *Medicine*, 2019; **98(5):**5(E14350).
23. Arzu Vicdana, Kubilay Vicdanb, Serdar Gunalpc, Aykut Kencea et al. *European Journal of Obstetrics &Gynecology and Reproductive Biology*, 2004; **117(1):**49-54.
24. Walid Al-Achkar, Abdulsamad Wafa, Faten Moassass. *Biomedical Reports*, 2013; **1(2)**:275-279.
25. Khan FH, Ganesan P, Kumar S. *Chemosphere*, 2010; **80(9):**972-977.
26. Siddiqi S, Siddiq A, Majeed K, Mansoor A et al. *Int. J. Agric. Biol.*, 2009; **11:**110-112.
27. KimSy, Kim Hj, Lee By, Park Sy et al. *J Reprod Infertil*, 2017; **18(3):**307-315.
28. Florina Raicu, Popa L, Pompilia Apostol, Cimponeriu D et al. *J.Cell.Mol.Med.*, 2003; **7(1):**43-48.
29. Carolina Gonçalves, Mariana Cunha, Eduardo Rocha, Susana Fernandes et al. *Asian Journal of Andrology,* 2017; **19(3):**338-345.
30. Zakaria Mahran, Rabie Bedir, Mekky Abdel Monem, Osama Shahat. *Trends In Medical Research*, 2017; **12:**20-25.
31. Raheleh Masoudi, Liusa Mazaheri-Asadi, Shahryar Khorasani. *Molecular Biology Research Communications*, 2016; **5(4):**247-255.
32. Pina-Neto JM, Carrara RCV, Bisinella R, Mazzucatto LF et al. *Braz J Med and Biol Res,* 2006; **39(4):**555-561.
33. Jon L Pryor, Marijo Kent-First, Ariege Muallem, Andrew H. Van Bergen et al. *The New England Journal of Medicine,* 1997; **336(8):**534-539.
34. Masashi Iijima, Kazuyoshi Shigehara, Hideki Igarashi, Koichi Kyono et al. *Asian Journal of Andrology,* 2019; **21:**1-4.
35. Rama Devi Mittal, Gunjana Singh, Aneesh Srivastava, Mandakini Pradhan et al. *Annales De Génétique*, 2004; **47(4):**331-337.
36. Sandeep Kumar Bansal, Deepika Jaiswal, Nishi Gupta, Kiran Singh et al. *Scientific Reports*, 2016; **6:**197-98
37. Dwi Anita Suryandari, Nukman Moeloek, Mila Citrawati, Puji Sari et al. *Makara, Kesehatan,* 2006; **10(1):**41-46.
38. Zhou R, Cheng J, Ma D, Tan Jet al. *Front. Genet*.2019; **10:**427.
39. Chylíková B, Hrdlička I, Veselá K, Řežábek K et al. *PLOS One*, 2016; **11(6):**E0156102.
40. Kovacheva K, Kotsev R, Emiliana Konova E, Rilcheva V, et al. *J of Imab*, 2018; **24(4):**2217-2222.
41. Asadi F, Sadighi Gilani Ma, Ghaheri A, Roodgar Saffari J, et al. *Cell J*, 2017; **19(1):**27-33.
42. Shailesh Pande, Pratiksha Chheda, Dollar Goradia, Tavisha Dama et al. *International Journal of Medical and Health Research*, 2018; **4(9):**109-112.
43. Ali Hellani, Saad Al-Hassan, Muhammed A Iqbal, SerdarCoskun. *Journal of Experimental & Clinical Assisted Reproduction*, 2006; **3:**1.
44. Yuan Pan, Hong-Guo Zhang, Qi Xi, Han Zhang et al. *Journal of International Medical Research*, 2018; **46(1):**307-315.
45. Venkatesh S, Thilagavathi J, Kumar K, Deka D, et al. *Arch Gynecol Obstet*, 2011; **284(6):**1577-1584.
46. Mojtabanezhad Shariatpanahi A, Ahmadnia H, Torkamanzehi A, Mansouri Torshizi M, et al. *Int J FertilSteril.*, 2018; **11(4):**253-257.
47. Sarah K Girardi, Anna Mielnik, Peter N Schlegel. *Human Reproduction*, 1997; **12(8):**1635-1641.
48. Shalaka S Ramgir, Aditi Sharma, Master Kruyanshi, AnamikaJaiswal et al. *IOP Conf. Series: Materials Science and Engineering*, 2017; **263:**22-33.
49. Ashraf J Shaqalaih, Masood S Abu Halima, Mohammed J Ashour, Fadel A Sharif. *J ExpClin Assist Reprod*, 2009; **6**:7-15.
50. Ghorbian S, Saliminejad K, Sadeghi, Javadi G et al. *Iranian Red Crescent Medical Journal*, 2012; **14(6):**358-362.