IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 8 Ver. II (Aug. 2014), PP 83-88
www.iosrjournals.org

The Cytogenetic Basis of Human Infertility: A Review

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Abstract: *Infertility resulting in humans has evoked considerable legal, medical and social interests. Infertility remains a major public health problem. Epidemiological studies reveal that genetic and environmental factors are responsible for infertility. As an estimate nearly 15-20% of couples have difficulty or is unable to conceive. Infertility is multi-factorial, but primarily it is because of male factor, female factor or a combination of both. Infertility can be hormonal, related to age, obesity, and infectious diseases, psychological or genetic. The genetic causes of infertility can be Y chromosome deletion, single gene disorder, multi-factorial causes and chromosomal abnormalities. The incidence of autosomal chromosome abnormalities is 1.1 to 7.2% in infertile men, about 3% in the azoospermia group and up to 10.2% in the oligozoospermia group. Genetic research on infertility aims to correlating clinical consequences and genotype.*

Key words: *azoospermia, chromosomal aberrations, cytogenetics, infertility, syndromes, Y chromosome microdeletion.*

I. Introduction:

Infertility is the most significant human health problem of the reproductive years. Infertility is described as failure to conceive after one year of unprotected intercourse[1]. The World Health Organization has described "infertility" as a health problem of global concern, one in seven couples experience infertility[2]. Shah et al. have also reported that one in every six couples wishing to start a family fall into this category[3].

The prevalence of infertility is reported to be 10-15% worldwide. It is estimated that infertility affects nearly 50 to 80 million people around the world[4]. Currently 8-10 million infertile couples are estimated to be in India. The recent National Family Health Survey estimated childlessness as 2.4% of currently married women over 40 years of age in India[5].

Primary and secondary infertility rates have been reported as 3% and 8%, respectively[6]. A village level study conducted in the state of Maharashtra, India revealed infertility in the range between 6 to 7 per cent[7]. In other states such of Haryana, Rajasthan, Madhya Pradesh, Punjab, Karnataka, Arunachal Pradesh and Tamilnadu have 2.25%, 3.57%, 4.23%, 4.93%, 6.73%, 8.72% and 10.92% childless couples respectively[8]. In the same study, 6% of male infertility and 14% of ovarian failure have been reported due to chromosomal abnormalities.

Infertility is multi factorial, but mainly it is because of male or female factors or a combination of both. Infertility can be hormonal, related to age, exercise, obesity or infectious diseases. It can be immunological, psychological, result from surgery or blockage or may be associated with defined abnormalities in the gametes. The most common causes of infertility are simply 'unexplained' and these account for about 20% of such couples[9].

II. Chromosomal Abnormalities:

The chromosomal abnormalities found in infertile couples are numerical or structural. Gianotten et al., reported that over 4,000 genes are involved in the control of human spermatogenesis[10].

I. Numerical abnormalities

1) **Klinfelter's syndrome (47, XXY):** Klinfelter's syndrome is found in approximately 1 in 1,000 males and due to non-disjunction of the X chromosome during meiosis. This syndrome is generally associated with the karyotype 47, XXY, which can be in all cells or in mosaic form. There are various extents of spermatogenetic failure, but males are generally sterile[3,11,12].

The gonadal defect in XXY male seems to be related to germ cell survival and sex chromosome constitution. It is through that the testicular atrophy seen in patients with Klienfelter's syndrome is due to failure of the germ cells, containing two X chromosomes (instead of one) to survive [13]. Beside this, the spermatogenic picture of XYY men shows a great diversity, ranging from severe impairment to apparent normalcy[14]. Other sexual numerical changes mainly involved other types of Klienfelter mosaics (45 X/47, XYY; 46, XY/47, XXY/48, XXXY) and 47, XYY males. These changes were seen in azoospermic and oligozoospermic males[15].

2) 47, XYY males: 47, XYY syndrome is found in approximately one in 1,000 male births. This syndrome arises due to non disjunction of the Y chromosome in paternal meiotic II. In 47, XYY male causes an aberrant hormonal balance in the gonadal environment which affects the normal function of human chorionic gonadotrophin[16]. Inclusion of extra sex chromosome (47, XYY) has been reported by May et al., Hassold et al. and Jacobs et al.[17,18,19].

3) **Turner syndrome:** A loss of X chromosome (45, X) is the characteristic karyotype of Turner syndrome. Frequency of Turner syndrome is one in 5,000 to one in 10,000[20]. Loss of chromosomes (X) resulting in numerical changes may be due to non-disjunction of chromosomes during gametogenesis. Due to non disjunction there is a possibility that a particular pair of chromosomes is transmitted to a gamete or it may be lost. There can be error in the gametogenesis due to the accumulation of mutations which might have taken place during the life span of an individual. These mutations are likely to be more in persons with advanced age.

4) **47, XXX:** The frequency of 47, XXX is one in 1,000 females and 95% of cases the extra X chromosome is maternal origin. Most these females are normal height, weight and mental function and fertile but have an early onset of menopause at about age of 30 years compared with the average of about age of 50 years[17].

5) **Down syndrome (Trisomy 21):**

Trisomy 21 is the most common cause of mental retardation, sexual dysfunction in humans. Affected females in rare cases can reproduce, however, most if not all, affected males are sterile, and the phenotype included spermatogenic arrest, reduction in the number of germ cells and bronchial tubes[21].

II) Structural abnormalities:

1) Translocation: Robertsonian translocations are among the foremost common balanced structural rearrangements seen within the general population with a frequency in newborn surveys of regarding one in 1,000[22]. Tharapel et al. reported that an approximately seven fold excess of Robertsonian heterozygotes in infertile couples[23]. In autosome-autosome translocation, reduce fertility is mediated by the fact that the translocated chromosomes, in order to progress through meiosis, need to synapse through a pairing cross[24,25].

The most common Robertsonian translocation observed in infertile males is t(13q14q). Meiotic studies of infertile carriers of t (13q14q) and t (14:21) reveal abnormal behavior of the rearranged autosomes in meiosis during spermatogenesis causing infertility[3, 26,27].

2) **Inversion:** An inversion happens when a solitary chromosome experiences two breaks and is reconstituted with the fragment between the breaks inverted. The result of inversion is for the offspring, a carrier of either kind of inversion is at risk of producing abnormal gamete.

The most widely recognized reversal is 46, XY, inv (9) (p11q13) in oligozoospermic infertile male. Nemeth et al.reported an infertile man with a Klinefelter like phenotype having an X inversion with 46,Y,inv(X) (q12q25)[28].

Dar et al.reported that a woman had dysgenesis with primary amenorrhea and she had a de novo inv (X) (q13 q24)[29]. Pericentric inversion of chromosome 1, 3, 5, 6 and 10 are related to abnormal sperm production in infertile men.

3. **Marker chromosome**: Marker chromosome is very small, unidentified chromosome. Marker chromosomes are additional chromosomes that are not effectively recognized by typical cytogenetic methods. Marker chromosome is occasionally seen in chromosome preparation, frequently in a mosaic state. Chromosome banding it is difficult to characterize marker chromosome. Carriers of marker chromosomes are at risk of infertility because of meiotic arrest and instability[25].

Table I: Cytogenetic studies in different infertile couples.

S. No.	Author	Year	Male karyotype	Female Karyotype	Abnormal karyotype in males (%)	Abnormal karyotype in females (%)
1.	Hens et al.[30]	1988	500	500	0.8	1.8
2.	Lange et al.[31]	1990	72	72	2.8	15.3
3.	Baschatt et al.[32]	1996	32	--	6.2	--
4.	Peschka et al.[33]	1996	200	200	3.0	3.0
5.	Testart et al.[34]	1996	261	261	4.2	1.1
6.	Mau et al.[35]	1997	150	150	12.0	6.0
7.	Montag et al.[36]	1997	434	434	3.7	3.7
8.	Meschede et al.[37]	1998	432	436	2.1	5.5
9.	Scholtes et al.[38]	1998	1116	1164	4.5	9.8
10.	Tuerlings et al.[39]	1998	1792	--	4.0	--
11.	Van der Ven et al.[40]	1998	305	305	3.3	3.3
12.	Peschka et al.[41]	1999	781	781	2.6	5.8
13.	Gekae et al.[42]	2001	2196	1012	6.1	4.8

14.	Alkhalaf et al.[43]	2002	118	--	10.16	--
15.	Carp et al.[44]	2004	458	--	9.60	--
16.	Quilter[45]	2005	103	--	9.7	--
17.	Lissitsina et al.[1]	2006	27	--	18.5	--
18.	Gagare et al.[46]	2012	112	--	11.6	--
19.	Drugkar et al.[47]	2013	70	--	12.85	--

4. **Microdeletion of Y chromosome**:

The variation of Y chromosome size in human is well known and there have been studies on the correlation of Y chromosome size with mental state, behavioral disorders and miscarriage[48].

Debraekeleer and Dao had reviewed several series reported on the type and the frequencies of chromosome abnormalities based on the type of male infertility problems. They also provided data on the relationship between meiotic abnormalities and male infertility[15]. The underlying genetic basis of male infertility remains largely unknown. It has been reported that 13.7% of azoospermia males and 4.6 % of severe oligozoospermic males have abnormal karyotype[49]. Genes located on the long arm of Y chromosome of men are likely to be involved in the complex process of spermatogenesis[50].

Azoospermic factor (AZF) due to microdeletion of the long arm of the human Y chromosome involving three regions is associated with complete absence of spermatozoa or reduced sperm count[51].

Table II: AZF gene region and their phenotype.

S. No.	Gene region	Candidate genes	Phenotype
1	AZFa	USP9Y DBY	Absence of germ cells, aka sertoli cell only syndrome (SCOS)
2	AZFb	EIF1AY RBMY (RBMYA1)	Maturation arrest at spermatocyte stage
3	AZFc	DAZ CDY1 BPY2 PRY TTY2	Variable from SCOS to severe oligospermia

The frequency of Y chromosome structural rearrangements was found to be higher than the frequency observed in newborn series. Much has been said on the possible deleterious effects of short and long Y chromosome (Yq^- and Yq^+) but no definite conclusions were drawn[52]. These rearrangements were preferentially seen in azoospermia and severe oligozoospermia (Sperm count $<10x10^6$/ml) exhibiting 1 and 0.6% respectively. A few cases of Y chromosome structural rearrangements involved failure of pairing between the X and Y-chromosomes. These include a dicentric Y chromosome and a pericentric inversion of the Y chromosome. Several oligozoospermic males were found to have a deletion of the long arm of the Y chromosome[53,54].

Table III: Y chromosome microdeletion in different infertile males.

S. No.	Author	Year	No. of patients	No. of deleted patients	Microdeletion (%)
1.	Tse et al.[55]	2000	58	4	6.90
2.	Tzschach et al.[56]	2001	97	0	0.00
3.	Peterlin et al.[57]	2002	226	10	4.42
4.	Dada et al. [58]	2003	83	8	9.64
5.	Athalye et al.[59]	2004	100	12	12
6.	Medica et al.[60]	2005	105	1	0.95
7.	Hsu et al.[61]	2006	460	24	5.22
8.	Mohammed et al.[62]	2007	266	7	2.63
9.	Balkan et al.[63]	2008	80	1	1.25
10.	Ceylan et al.[64]	2009	90	11	12.22
11.	Stahl et al. [65]	2010	1591	149	9.37
12.	Behulova et al.[66]	2011	226	8	3.54
13.	Kim et al. [67]	2012	1306	101	7.73
14.	Chellat et al.[68]	2013	80	1	1.25
15.	Omar et al.[69]	2014	36	3	8.33
16.	Yuanyuan et al.[70]	2014	1218	105	8.62

III. Syndromes

Many genetic syndromes associated with infertility in humans, such as Noonan syndrome, immotile cilia syndrome, Kallmann syndrome, Androgen insensitivity syndrome, polycystic kidney diseases, ushers syndrome etc.

Table IV: Some genetic syndromes associated with infertility.

S. No.	Genetic syndrome	Incidence	Inheritance	Features	Reference
1.	Androgen insensitivity syndrome	1:60,000	X linked recessive syndrome	Mild spermatogenic defect, present at birth with ambiguous genitalia and signs of both male and female sexual development. Caused by mutations in AR gene	Patrizio and Broomfield[21]
2.	Frasier syndrome and Denys-Drash syndrome	1:10,000	Autosomal dominant	Renal failure, Wilm's tumor, hypertension, gonadal dysgenesis. Caused by mutation in the WT1 gene.	Swain and Lovell-Badge[71]
3.	Kallmann syndrome	1:10,000-60,000	X linked, Autosomal dominant	Delayed or absent puberty and an impaired sense of smell. Caused by mutation in the KALIG-1 gene.	Nudell and Turek[72]
4.	Noonan syndrome	1:1000-2500	Autosomal dominant	Congenital heart defect, hypertrophic cardiomyopathy, short stature, learning problems, pectus excavatum, webbed nack and flat nose bridge. Caused by mutation in the PTPN11 gene.	Tartaglia et al.[73]
5.	Polycystic kidney disease	1:800	Autosomal dominant	Progressive cyst development and bilaterally enlarged kidneys with multiple cysts. Caused by mutations in the PKD1, PKD2 and PKHD1 genes.	Patrizio and Broomfield[21]
6.	Ushers syndrome	1:30,000	Autosomal recessive	Combination of hearing loss and visual impairment, leading cause of deaf-blindness and degeneration of the sperm axoneme. Caused by mutations in the CDH23, MYO7A, PCDH15, USH1C, USH2A, GPR98 genes.	Patrizio and Broomfield[21]

IV. Conclusions

Infertility is multi-factorial, but primarily it is because of male factors, female factors or a combination of both. Chromosomal anomalies in infertile subjects may be numerical and structural aberrations. Infertility resulting in men has evoked considerable legal, medical and social interests. Currently, the strongest known genetic marker for infertility leading to violent attitude in some men is the Y chromosome. Genetic research on this disorder aims at correlating phenotype and genotype. The elucidation of such correlations helps us to achieve a more thorough understanding of infertility in couples. The meaningful genotype-phenotype correlation can only image if sufficient attention is paid to sound documentation of the genotype and consequent clinical phenotype.

The underlying genetic basis of infertility remains largely unknown. Cytogenetic studies particularly on sex chromosome with special reference to Y chromosome in men are required to be explored.

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