MOLECULAR GENETIC OF MALE INFERTILITY: A NEW THERAPEUTIC PERSPECTIVES

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ABSTRACT

Infertility is an ailment of the regenerative system portrayed by failure to accomplish pregnancy following 12 or more months of consistent unprotected sex. A variety of variables, including ovulation imperfections, spermatogenic failure, parental age, heftiness, and infections have been connected with Infertility, notwithstanding particular karyotypes and genotypes. The hereditary of Infertility is an inconceivable subject, and the hereditary reasons for a few regenerative issue are chromosomal, include single genes, or are polygenic. What's more, there are a few hereditary disorders that show Infertility. In spite of broad investigations, there are no well-defined genes that can be utilized for genetic testing of Infertility conditions. Henceforth, there is a requirement for novel diagnostic techniques to distinguish both new and known Infertility genes. At present, a few genetic association investigations have been performed to distinguish genes for Infertility. Expanding the specimen size of these association investigation may amplify the shot of distinguishing solid associations of gene responsible for infertility. Whole genome sequencing can be considered, particularly in idiopathic instances of Infertility, in spite of the fact that translation of high throughput sequencing information might itself be a tough challenge. Moreover, genotype and phenotype correlated studies and microarray-based GWAS studies from substantial number of subjects could reveal more light into the genetic reasons for Infertility syndrome. Bisulfite sequencing, methylated DNA immuno-precipitation sequencing, and methylated DNA capture by affinity purification sequencing may help future examinations. In the future,
seeking the most encouraging genetic variations, transformations, or polymorphisms may give clinically pertinent therapeutics to infertile subjects.

**KEYWORDS:** Infertility, microdeletions, chromosome, ART, spermatogenesis, ICSI, microdeletions.

**INTRODUCTION**

Infertility is a worldwide marvel that influences between 70 million and 178 million individuals worldwide.\(^1\)-\(^3\) It influences up to 15% of couples worldwide, which places an enormous mental burden on the infertile couple, particularly on the lady, and it may prompt depression, suicidal inclinations, and other mental conditions.\(^4\) The involvement of male factors to Infertility is ~30-half. Past studies showed that environmental and hereditary variables are involved in the abatement of the regenerative potential in male. The primary genetic elements involved in male Infertility are chromosomal variations and Y-chromosomal microdeletions inside of the Yq11 region. The genes controlling spermatogenesis is situated in the Yq11 region termed as azoospermia factor genes (AZF). The occurrence of cytogenetic variations has been evaluated to be 3-30 % in infertile men and just 0.6-1% in the general male population.\(^5\)-\(^7\) Chromosomal anomalies in the infertile male may be numerical or structural and include sex chromosomes (e.g., 47, XXY) or autosomes (e.g., Robertsonian translocations). Around 10% of the oligozoospermic and 15% of the azoospermic cases harbor genetic variations.\(^8\)

Genetic testing permits elucidating a dark Infertility diagnosis, as well as averts miscarriage and iatrogenic transmission of genetic defects to the posterity by ART.\(^9\)-\(^11\) The most essential strength of genetic testing lie in its capacity to distinguish men with genetically defective sperm along these lines helping couples settle on informed reproductive decisions. Previously, large structural chromosomal distortions, characterized by karyotype investigations, were recognized.\(^12\) Utilizing modern testing much smaller genomic regions has been observed to be accountable for Infertility. Of the four subjective compartments, genes communicated in the gonad include the most well-known site influenced by transformations causing Infertility.\(^13\)-\(^15\) Researcher ought to know about the most widely recognized reasons that have clinical ramifications:

- Ladies with a 45,X cell line usually have heart abnormalities that may represent a risk for maternal demise in pregnancies accomplished by donor egg IVF.
Men with Y-chromosome deletions may produce male child with the same deletion, interpreting them Infertile; CBAVD must be learned in men with azoospermia due to the risk for having a kid with CF; and A few ladies with premature ovarian failure may be fragile X disorder carrier, so other relatives may be at risk for higher inheritance of the syndrome.

Recently, more genes have been recognized which bring Infertility in people. In selected cases, where hereditary deformity is known, it might be conceivable to utilize preimplantation genetic diagnosis to screen embryo before uterine transfer. At present, the standard technique of particular gene sequencing, mutation investigation and sperm epigenome are constrained by a few components including expense, accessibility, and clinical relevance. Microarray technology, which assesses for CNV, gene expression levels and SNP, has yielded a few male fertility gene candidates with solid relationship in Infertility and sperm gene(Table 1). Microarray technologies have additionally empowered assessment of sperm messenger RNA that correspond with spermatogenesis, sperm motility, histone modification, germ cell anti-apoptotic process, DNA repair, and oxidative stress reduction. Latest investigations have demonstrated that the mRNA profiles contrast in sperm that succeed or fail to bring about pregnancies in ART.

**Table: 1 Infertility diagnosis with latest technique**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Specimen Tested</th>
<th>Principle</th>
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<tbody>
<tr>
<td>Karyotype</td>
<td>Peripheral blood</td>
<td>Assess number and appearance of eukaryotic cells</td>
</tr>
<tr>
<td>FISH</td>
<td>Peripheral blood</td>
<td>Detect chromosomal aneuploidy and structural abnormalities</td>
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<tr>
<td>Microarray</td>
<td>sperm</td>
<td>Analyze CNV, gene expression level, SNP and mRNA transcript pool expressed by sperm</td>
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<td>Next Generation sequencing</td>
<td>Peripheral blood</td>
<td>Detect DNA methylation problems</td>
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<tr>
<td>Gene Sequencing for mutation</td>
<td>Peripheral blood</td>
<td>Determine gene sequencing and mutation using dye terminator sequence</td>
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<td>and polymorphism analysis</td>
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**Identification of meiotic imperfections in Infertile couples**

Notwithstanding somatic imperfections influencing fertility, meiotic recombination variations can be a reason for human Infertility and aneuploidy. Transformation that lessen or
nullify recombination are linked with meiotic arrest, abnormal chromosomal segregation and increased nondisjunction. Recombination procedures are developmentally moderated. Decreased recombination is connected with all trisomic conditions, including Down's disorder (trisomy 21), Edward's disorder (trisomy 18), Patu's disorder (trisomy 13), non-obstructive azoospermia and male Infertility because of sperm aneuploidy.[24]

Most aneuploidy happens amid maternal meiosis I, with advanced maternal age being a known risk element. The second most vital risk element is decreased recombination amid meiosis. The temporal controls of recombination contrast by gender, and recombination rates can even fluctuate between ova. Since meiosis in ladies is hard to investigate, as it for the most part happens in utero and amid initiation of fertilization, human aneuploidy studies have concentrated on spermatogenesis.[25] Scientists have initially reported sperm aneuploidy in infertile men with a typical somatic karyotype happening because of defective meiosis amid spermatogenesis. Regardless of studies demonstrating that infertile men have a high frequency of aneuploid sperm, the issue of sperm aneuploidy has been to a great extent overlooked in the assessment of infertile couples.[26-28] Sperm aneuploidy may account, to some extent, with higher rate of sex chromosome deformities in children brought about by ICSI, the higher rate of pregnancy loss after testicular sperm extraction with ICSI for treatment of non-obstructive azoospermia and repetitive pregnancy loss in a few couples with unexplained infertility. Aneuploid ova or embryos might likewise underlie recurrent pregnancy loss.[29]

Y chromosome microdeletions
Microdeletions in the Y chromosome long arm (Yq) signify the most common genetic reason for severe infertility observed with a pervasiveness of 15% in non-obstructive azoospermia and 10% of extreme oligozoospermia.[30] Most of the deletions are found in men with a sperm count beneath $2 \times 10^6$/ml. Three locales, alluded to as 'azoospermia factors' (AZFa, b and c from proximal to distal), have been defined as spermatogenesis loci. The hereditary pathways and mechanisms of spermatogenic impairment in men with Yq microdeletions are obscure. The function of AZF genes in spermatogenesis is likewise not clear, and the molecular mechanism which is altered in AZF deletion is totally obscure. The larger part of Y microdeletions deliver the concurrent loss of a few genes mapped inside AZFb and AZFc loci.[31-32]
AZFa deletions are uncommon and include just two genes, USP9Y (ubiquitin specific peptidase 9, Y-linked) USP9Y (ubiquitin specific peptidase 9, Y-linked) USP9Y and DBY (DEAD box polypeptide 3, Y-linked). A large portion of the DBY AZF microdeletions are produced by intra-chromosomal homologous recombination between repeated sequences palindromic structures demonstrating identical sequence. The complete AZFc deletion, b2/b4 deletion, removes eight gene families including all individuals from the DAZ (deleted in azoospermia) gene family, which is the strongest candidate of the AZFc. Deletions in the AZFa region typically prompt Sertoli cell syndrome, complete deletion of AZFb or AZFb+c lead to azoospermia connected with Sertoli cell-syndrome or pre-meiotic spermatogenic arrest.[33]

The most frequent AZFc deletion prompts azoospermia or extreme oligozoospermia, connected with diverse spermatogenic phenotypes in the testis. Overall, 70% of such men have spermatozoa in the discharge or in the testis.[34-37] Most men with Yq microdeletions require ICSI to defeat their Infertility. Since all spermatozoa from Y-deleted men harbor the same microdeletions, ICSI permits the transmission of such microdeletions. Male children of men with Yq microdeletions will likewise carry the deletion and will have spermatogenic disability in adulthood. Recent investigation has shown that men with AZFc likewise deliver a higher rate of spermatozoa with aneuploidies.[38] In the patients with AZFc deletion had a significant diminishment in the rate of normal Y-bearing spermatozoa compared and normozoospermic control men, a corresponding increase in nullisomic spermatozoa and a significant increase of XY-disomic spermatozoa was identified.[39]

Consequently, AZF microdeletions can be considered as 'pre-mutation' for complete loss of the Y chromosome in the AZF-deleted patients’ spermatozoa, expanding the risk of embryonic X0 cells.[40] Although no genital variations or other somatic defect in the ICSI-AZFc children are accounted, genetic counselling ought to consider the perceptions of sperm sex chromosome aneuploidies in these men, and the conceivable increased risk of developing 45,X (Turner's syndrome) or 47,XXY embryos (Klinefelter's syndrome).[41] It must be noted, that these risk are more hypothetical in light of the fact that in the 31 children officially conceived from men with AZF deletion, no results other than transmission of the Yq deletion have been accounted. All things considered, clear data in regards to implantation rate and incidence of fetus removal for the accomplices of men with Yq microdeletions is not yet accessible.[42-44]
Genetic Disorder of male infertility

Spermatogonial sequences are kept in an idle state inside the fetal testis until puberty when they expand in number by repeated mitotic divisions. Spermatogenesis initiate in adolescence and is controlled by various genetic factor.\textsuperscript{[45-46]} It has been assessed that 2000 genes are vital for the full procedure to be finished; of these, just 30 genes are available in the Y chromosome Genetic anomalies including chromosomal variations and monogenic disorder have been assessed to react in 15% of Infertility cases. Infertile men with genetic alterations normally give impeded spermatogenesis, genital structural abnormalities, diminished testicular size, hypogonadism and sperm dysfunction. Although its predominance is obscure, genetic variations might likewise happen in male with UMI.\textsuperscript{[47]}

Pedantically, genetic anomalies can be assembled into four fundamental categories:

- Chromosomal imperfections in the somatic cells;
- Gene transformation and polymorphisms in the substantial cells;
- Sperm chromosomal variations; and
- Epigenetic syndrome.

In spite of the fact that the initial two classifications influence men with anomalous genotypes in substantial cells, sperm chromosomal variations can be started from people with either normal or abnormal genotypes. Epigenetics, alludes to the mitotically or meiotically heritable changes in gene function that can't be clarified by changes in DNA sequence.\textsuperscript{[48-50]}

Genetic tests in unexplained male infertility

Male Infertility represents half of all Infertility cases. Male Infertility can be a multifactorial issue. In 40% of cases, the reason for Infertility is unknown. The genetic reasons incorporate chromosomal variations, mitochondrial DNA transformations, and endocrine disorder.\textsuperscript{[51-53]} Chromosomal distortions and SNP represent 15% of male infertility. The nongenetic reasons incorporate hypogonadism, testicular maldescent, and structural anomalies in the male genital tract, infection, feebleness, chronic ailment, and immunological conditions.\textsuperscript{[54]}

Gene transformations

A few hundred genes are vital for normal sexual development, testis determination, testis descent and spermatogenesis. On the other hand, just a couple have routine clinical significance.\textsuperscript{[55-56]} These incorporate the CFTR gene, whose transformations cause cystic fibrosis and absence of vas deferens, the androgen receptor gene, whose transformations cause the androgen insensitivity disorder and spermatogenic damage, and the INSL3 (insulin-
like factor 3) and LGR8 (leucine-rich repeat containing G-protein coupled receptor 8) genes, whose transformations have been connected with variations in testis descent (cryptorchidism).

There is general assertion that 70% of subjects with inborn bilateral absence of the vas deferens (CBAVD) have transformations in the CFTR gene, with no other clinical manifestations of cystic fibrosis.[57] Mutations in the androgen receptor (AR) gene on the X chromosome cause an assortment of deformities referred as androgen insensitivity syndrome (AIS). Besides, just a minority of Infertile male with lifted testosterone and LH (indicative for androgen insensitivity) had transformations in the AR gene, despite the fact that the higher the ASI (androgen sensitivity index, result of LH (testosterone), the more probable a transformation in the AR (Table 1). Hence, AR gene transformations may assume a part as hereditary reasons for male Infertility and are found with a pervasiveness of around 3% in unselected infertile men, with comparative frequency in azoospermia, serious oligozoospermia and moderate oligozoospermia.[58-59]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Infertility Disorder</th>
<th>Gene Responsible</th>
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<tbody>
<tr>
<td>1</td>
<td>Leydig Cell Hypoplasia</td>
<td>LHCGR</td>
</tr>
<tr>
<td>2</td>
<td>Spermatogenic Failure</td>
<td>RBYMIAI,BPY2,DBX3Y,HSFYI,SMYD3,CDY2A,PIWIL2</td>
</tr>
<tr>
<td>3</td>
<td>XY,Gonadal Dysgenesis</td>
<td>SRY,SFLDHH,C22ORF80,DMRTI,MAMLDI,SUPT3H,PRKACG,FAM189A2</td>
</tr>
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</table>

A few genes appeared to be more encouraging (MTHFR, DAZL, POLG, FSHR, ER-a). The protein 5-methylenetetrahydrofolate reductase (MTHFR) is included in the transformation of homocysteine to methionine.[60] A point transformation in its coding region (C677T) diminishes the action of the enzyme by around 35% in heterozygotes (CT) and 85% in homozygotes (TT). Likely negative impacts of the MTHFR (C677T) transformation on male fertility may be because of a modification in the expression of spermatogenesis genes affected by under methylation, or spermatozoa may be damaged by a higher production of lethal reactive oxygen metabolites leading DNA damage.[61]

**Closing Remarks**

Genetic variation leading to male Infertility are complex. Alongside gross chromosomal aneuploidies and mutations, microdeletions and SNP can meddle with male fertility. Male fertility is not just subject to genes controlling the male germ line but additionally on genes...
responsible for male gonad development and somatic cell development. It remains an overall issue challenge. Management of Infertility has been and still a troublesome medicinal errand not just on account of the difficulty in the diagnosis and treatment of the reproductive issue in every partner. The treating specialist who is guiding the couple in regards to their Infertility must be acquainted with the reasons, examinations and the available treatment options. The couple should be given sensible information about their shots of having a live birth, and in addition, the risk and expenses of the management plan and their alternatives.

Male fertility, including spermatogenesis and sperm function, is controlled by many genes. As men with unexplained Infertility can harbor genetic variations that may bargain their reproduction potential, endeavors ought to be made to distinguish such conditions. As of now, couple of diagnostic tools are accessible for routine use and their convenience is not yet totally clear. Chromosomal variations in substantial cells can be distinguished by karyotyping. Sperm aneuploidy assessment in couples with unexplained infertility encountering either repeated IVF failures or repetitive pregnancy loss can be performed by FISH while transformations and polymorphisms are recognized by gene sequencing. Numerous advances are as of now being made and the utilization of novel microarray technology may hold the way in precisely diagnosing and treating men with unexplained infertility.

Conflicts of Interest Statement
The Authors declare no conflicts of interest.

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