Janaki Medical College Journal of Medical Sciences (2025); Vol.13 (1):68-76

JMCJMS

Review Article

Genetics of Male Infertility

Nilam Thakur[1*], Ajit Saxena[2], Amar Prakash Garg[3]

Author's Affiliations

[1]Shobhit Institute of Engineering & Technology, Deemed to be University, Meerut
[2]AII India Institute of Medical Sciences, Patna, India
[3]Swami Vivekanand Subharti University Meerut, India

Correspondence to:
Dr. Nilam Thakur
Shobhit Institute of Engineering & Technology
Deemed to be University, Meerut, India
Email: drnilam.t@gmail.com

ABSTRACT

Infertility is defined as the inability to conceive after at least one year of regular, unprotected sex. This affects 15–20% of couples and estimated to affect 72.4 million people globally. According to WHO, 9% of couples worldwide struggle with fertility issues and the male factor accounts for 50% of couple sub-fertility with only responsibility in 30% of cases and a co-contributing female factor in 20% of factors. Male infertility is widely known to be partially caused by genetic disorders. Genetic abnormalities can affect spermatogenesis, hormone regulation, and reproductive tract development, leading to various forms of male infertility. This review paper provides an in-depth analysis of the genetic factors contributing to male infertility, including chromosomal abnormalities, single-gene mutations, and Y chromosome microdeletions.

Keywords: Male infertility, Chromosomal abnormality, Y Chromosome microdeletions.

INTRODUCTION

Infertility is defined as the inability to conceive after at least one year of regular, unprotected sex. This affects 15–20% of couples [1]. Globally, 72.4 million people are estimated to be affected whereas WHO estimates that 9% of couples worldwide struggle with fertility issues. The male factor accounts for 50% of couple sub-fertility with sole responsibility in 30% and a co-contributing female factor in 20% [2].

Etiology of Male Infertility

Male infertility can result from various factors, including anatomical abnormalities, hormonal imbalances, genetic disorders,

infections, and environmental or lifestyle influences. These causes are broadly classified into pre-testicular, testicular, and post-testicular categories, along with other contributing factors [3]. Pre-testicular causes (hypothalamic-pituitary axis disturbances) comprises; hypogonadotropic hypogonadism (e.g., Kallmann syndrome), hyperprolactinemia and pharmacological influences (e.g., hormone-altering drugs). The testicular causes (spermatogenic defects) involve various factors like varicocele (enlarged scrotal veins), cryptorchidism (undescended testes), testicular cancer or radiation exposure, chemotherapy or drug-induced damage, genetic disorders (e.g., Y-chromosome microdeletions, Klinefelter syndrome) [4], spermatogenic failure (e.g., sertoli cell-only syndrome), environmental factors (toxins, heat exposure), infections (e.g., orchitis), injury or trauma to the testes. Similarly, post-testicular causes (ductal obstruction/dysfunction) include obstructive azoospermia e.g. congenital bilateral absence of the vas deferens (CBAVD), ejaculatory duct obstruction, seminal vesicle dysfunction, vasectomy or iatrogenic injury to the vas deferens and ejaculatory disorders like retrograde ejaculation, nerve injury (e.g., spinal cord injury, retroperitoneal lymph node dissection), Young's syndrome (obstructive azoospermia with sinopulmonary infections), and immunological factors like Anti-sperm antibodies [5]. Other Contributing factors can have Systemic diseases (e.g., diabetes, chronic kidney disease), Primary ciliary dyskinesia (immotile sperm), Lifestyle factors (e.g., alcohol abuse, smoking, stress).

The genetic factors involved in male infertility can be chromosomal or monogenic disorders, mitochondrial DNA (mtDNA) mutations, Y chromosome deletions, multifactorial disorders, imprinting disorders, or endocrine disorders of genetic origin [6].

Chromosomal Abnormalities:

Chromosomal abnormalities include both numerical and structural chromosomal aberrations, which are large enough (>4–5 Mb) to be discerned under the microscope. They account for 5%–10% cases of oligozoospermia [7], to 15%–25% cases with nonobstructive azoospermia [7,8]. Karyotyping was the first test used to look for genetic abnormalities in infertile males, and it is still the most common diagnostic test for male infertility today.

Numerical Aberrations: Numerical chromosome errors are a frequent cause of male infertility. The incidence is inversely proportional to the number of sperm in ejaculate. Klinefelter syndrome (KFS) is the most common numerical chromosomal abnormality and is the most common cause of azoospermia. It is found in 11% cases with azoospermia. Men with 47,XXY chromosomal complement are azoospermic due to seminiferous tubule dysgenesis, whereas mosaic cases with normal 46,XY cell line may be oligozoospermic. Likewise, 46,XX male affects 1 in 20,000 men. During paternal meiosis, aberrant translocation of Y material, including sex determining region (SRY) to the X chromosome leads to the 46,XX male chromosomal complement. Presence of SRY gene results in testicular differentiation but absence of spermatogenesis due to absence of long arm of Y chromosome [6].

Structural Aberrations: Robertsonian translocations (RT) are found in 1 in 1000 individuals (6) and are the most common structural rearrangements in infertile men. RT result in the fusion of the long arm of 2

acrocentric (Group D chromosomes: 13, 14, 15 and Group G chromosomes: 21, 22, and Y) chromosomes. The fused short arms are mostly lost, and hence the carrier has a chromosomal constitution with 45 chromosomes. Reciprocal translocations occur when there is exchange of genetic material between nonhomologous chromosomes. It affects 1.17% of infertile men [9]. Inversions are balanced structural rearrangements found in 10%–15% of prenatal diagnosis and 0.1% of infertile men [9]. Inversions can be paracentric or pericentric. Paracentric inversions occur when both breakpoints are on one chromosome arm and do not involve the centromere. Pericentric inversions occur when the chromosome breaks include the centromere and the short and long arm of the chromosome. Germline mosaics are men with a normal somatic karyotype but an abnormal cell line in their germ cells. They are discovered only on a testicular biopsy. Studies have discovered that 1%–17% of infertile men have germline mosaicism [10].

Germline mosaics: Germline mosaics are men with a normal somatic karyotype but an abnormal cell line in their germ cells. They are discovered only on a testicular biopsy. Studies have discovered that 1%–17% of infertile men have germline mosaicism [6].

Genes associated with male infertility:

Karyotype analysis was also essential to identify the location of genetic factors controlling normal spermatogenesis. It was through the usage of this technique that in 1976 a deletion at the distal portion of band q11 of the Y chromosome was found in 6 men with azoospermia and the region was identified as essential for spermatogenesis [11].

Y- chromosome genes:

Y chromosome is one of the smallest human chromosomes (60 Mb) and is highly polymorphic in length. It is male specific and the only haploid component of the human genome. Till now 156 transcription units, 78 protein coding genes, and 27 distinct proteins (9 on Yp and 18 on Yq) encoded by the Y chromosome have been identified. The Y chromosome is divided into 7 deletions intervals. The region critical for spermatogenesis is on interval 5 and 6. The length of euchromatic DNA sequences on the Y is about 23 Mb, including 8 Mb on the short arm and 14.5 Mb on the long arm. There are 3 classes of euchromatic sequences those transposed from the X chromosome during the process of the evolution of the Y (X-transposed), those similar to sequence information from the X chromosome (X-degenerate), and those repeated units across the proximal short arm of the Yp and across most of the Yq (amplicons). Within the X transposed segments, only 2 protein-encoding genes have been identified (TGIF2LY and PCDH11Y). The X-degenerate regions, with a combined length of 8.5 Mb, are dotted with single-copy genes or pseudogenes that are mostly expressed ubiquitously (i.e., expressed in multiple organs in the body and not confined to a specific tissue). The sex-determining gene (SRY) is located in this region. The SRY gene expresses a transcription factor that switches on the genes for male sexual differentiation [12].

Microdeletion of the Y- Chromosome:

Microdeletions on the long arm of the Y chromosome (Yq) is one of the most significant pathogenic defects associated with male infertility. Tiepolo and Zuffardi in 1976,

hypothesized a correlation between Y chromosome deletions and male infertility [11]. Yq microdeletions are found in 13% azoospermic men, 1%–7% severely oligozoospermic men (sperm count less than 0.5 million/mL). These deletions are clustered in interval 5 and 6 of the Y chromosome. It was defined as Azoospermia Factor (AZF) as the most severe phenotype associated with its deletion was azoospermia. The AZF region is further subdivided into 3 nonoverlapping regions termed as AZFa, AZFb, and AZFc. Six genes located in the AZF regions are expressed exclusively in the testes and are therefore known as "AZF candidate genes." The AZFa spans around 400–600 kb of DNA and is located in the proximal portion of deletion interval 5. AZFa region harbors 2 protein encoding genes, namely, USP9Y and DBY (recently termed DDX3Y). Deletions of AZFa loci is characterized by Sertoli-cell-only syndrome, type I. The AZFb spans around 1–3 Mb of DNA and is located on the distal portion of deletion interval 5 to the proximal end of deletion interval 6 (subinterval 5O–6B). Protein-encoding genes in AZFb region are EIF1AY, RPS4Y2, and SMCY that are located in X-degenerate euchromatin, and HSFY, XKRY, PRY, and RBMY that are in the ampliconic region. AZFb gene is expressed in primary spermatocytes and thus its deletion leads to the arrest of meiosis and manifests as maturation arrest with the accumulation of primary spermatocytes [13]. AZFc spans 3.5 Mb of euchromatin and is located at the distal part of deletion interval 6 (subinterval 6C–6E) on the Y chromosome [11]. Deletions of the AZFc region are most common in men with idiopathic oligozoospermia or azoospermia. AZFc region contains 8 gene families that are involved in spermatogenesis—BPY2, CDY, DAZ, CSPG4LY, GOLGAZLY, TTY3.1, TTY4.1, and TTY7. There are 4 copies of DAZ and it also has an autosomal homolog DAZL on 3p24. The first recognized gene in the AZFc was Deletion in Azoospermia factor (DAZ). This gene encodes RNA-binding proteins that are exclusively expressed in the germ cells [14]. A number of infertile men harbor partial deletions in AZFb and AZFc loci. Considering the Y chromosome structure and the complexity of the deletion mechanism involved, it is possible that few other deletions also supplement the effect of partial AZFb and AZFc deletions. Frequency and pathologic significance of these partial deletions is still not known. A partial 1.6 Mb deletion on Y chromosome, termed as "gr/gr" deletion specifically in infertile men with varying degrees of spermatogenic failure [15]. AZF deletions are specific for spermatogenic failure. The deletion of AZFa or AZFb loci and large deletions encompassing 2 or more loci lead to azoospermia and carry poor prognosis if such couples opt for ART. Cases with AZFc deletions have a variable phenotype and chances of sperm retrieval are high; however, such cases show progressive decline in sperm count over time and progress from oligozoospermia to azoospermia [16].

Autosomal Gene mutations in infertility:

The complex interaction of gene products on both the sex chromosomes and the autosomes are essential for the fertility of an individual. Several autosomal genes, such as acrosin gene, BAX, BCL16, c-kit, ATM, HSP70.2, RAD6B, MDHC7, CREM, and DNA11 and 12, play an important role in germ cell development and spermiogenesis. Mutations of CFTR gene on chromosome 7 leads to obstructive azoospermia and is found in 60%–90% of patients with congenital bilateral absence of vas deferens (CBAVD).

F508 del is the most common CFTR mutation found in 60%–70% of CBAVD patients [17]. The methylenetetrahydrofolate reductase (MTHFR) plays a critical role in folate metabolism, and is essential for DNA methylation and spermatogenesis. The gene for MTHFR is located on chromosome 1 and any mutation in the MTHFR may disrupt the methylation of the nucleotides in the germ cells, a very sensitive regulatory step for the accurate transmission of genetic information to the offspring [18].

Syndromes associated with male infertility:

Important syndromic cases linked to male infertility are KFS, AIS/IMS, KS, Kartagener syndrome, metabolic syndrome, Persistent Mullerian duct syndrome, Aarskog– Scott syndrome, Kearns–Sayre syndrome, Polyglandular failure syndrome types I and II, Bardet–Biedl syndrome, Noonan syndrome, Prader–Willi syndrome, deafness infertility syndrome [19].

Specific gene mutations resulting in male infertility:

The first gene linked to male infertility outside of the Y chromosome was identified in 1988 on chromosome X. At the time, mutations in the murine androgen receptor gene, mapped via linkage analysis to the X chromosome, had already been well established to cause testicular feminization in mice [20]. Centered on this information, Brown et al. in 1988 used a PCR-based approach coupled with southern blotting to reveal that deletion of the human Androgen Receptor (AR, also known as NR3C4) was responsible for infertility in patients with mild or partial androgen insensitivity syndrome, as well as sex reversal in patients with complete androgen insensitivity syndrome [21]. In 1989, mutations in the CFTR gene (Cystic Fibrosis Transmembrane Conductance Regulator) on chromosome 7 were discovered to underlie Cystic Fibrosis, using restriction fragment length polymorphism (RFLP) analysis to pinpoint the genomic locus of interest followed by PCR based sequencing to identify mutations [22]. In early 2000s, Optimization and upscaling of Sanger sequencing on automated DNA sequencers resulted in wide-scale adoption of DNA sequencing in human disease research and diagnostics [23]. It was particularly successful in testing for mutations in candidate disease genes identified by either positional cloning or by evidence from orthologous genes studied in model organisms. A good example of this was shown by the identification of mutations in SYCP3 gene related to meiotic arrest during spermatogenesis [24].

Editions made to existing sequencing technology as well as the introduction of single nucleotide polymorphism (SNP) microarrays in the 1990s permitted once more a shift in the research approaches available to investigate the genomes of infertile men and identify novel genes associated with male infertility. In 2007, this new positional cloning approach resulted in the identification of two novel male infertility genes, AURKC and SPATA16, causing multiple morphological sperm abnormalities [25].

Genomic copy number variation by Microarray:

The application of SNP microarray technology revealed one important CNV associated with male infertility in 2011, a 200 kb homozygous deletion affecting the DPY19L2 gene [26].

In 2011, Tüttelmann et al., [27] employed microarray technology to discover an excess

of rare CNVs on the sex chromosomes of azoospermic and severe oligozoospermic German men. Using a similar microarray approach, recurrent deletions affecting the DMRT1 gene located on chromosomes 9 have been associated with azoospermia [28]. While SNP and CGH microarrays have highlighted the important role of CNVs in male infertility, the widespread application of next-generation sequencing (NGS) now offers the opportunity to combine the detection of CNVs and other more complex structural variations with the simultaneous detection of SNVs [29,30]. Recently, a balanced reciprocal translocation affecting the SYCP2 gene was reported in a patient with severe oligozoospermia, initially discovered by karyotyping but further characterized using both microarrays as well as NGS [31].

Next-generation sequencing (NGS) to detect new disease genes:

The development of high-throughput NGS platforms in the past decade has resulted in a dramatic drop in sequencing costs and an equally dramatic increase in sequencing throughput. Rather than relying on the need to select and sequence individual candidate genes or evaluate specific polymorphisms or large structural defects in a small number of patients and controls, NGS allows for unbiased sequencing of large numbers of genes, all coding exons (whole exome sequencing) or sequencing of the entire human genome, and increasingly allows this to be done in very large cohorts of patients and controls.

NGS-based technology is a powerful tool for identifying the genetic basis of the human phenotype. As one of the leading molecular techniques in the field of reproductive medicine, Whole Exome Sequencing (WES) has a major impact on our understanding of the genetic causes of male infertility. WES generates a large amount of genetic data; however, the processing of WES data can be complex [32]. NGS has provided an inexpensive and rapid genetic screening approach to discover novel disease-associated genes [33]. In recent years exome sequencing has become the predominant technology used for disease gene studies in male infertility. Male factor infertility is an important clinical problem whose most severe phenotype, severe oligospermia or azoospermia, has a variety of genetic causes. Some, like Klinefelter syndrome or cystic fibrosis, are well understood, but most are still unknown, and Y chromosome microdeletions only explain a fraction of the remaining cases. In consanguineous and nonconsanguineous families, whole exome sequencing (WES) has been successfully used to identify likely causal mutations in severe oligospermia [34]. Exome sequencing has also been successfully applied to identify new disease genes for patients with acephalic spermatozoa. In particular, homozygous and compound heterozygous mutations in testis-specific genes BRDT, SUN5 and PMFBP1 have been found to disrupt the head-flagella junction of the spermatozoa of these infertile men [35]. NGS has also been instrumental in the study of congenital isolated hypogonadotropic hypogonadism, characterized by incomplete or absent puberty and infertility. A large number of pathogenic mutations have been identified in genes and genetic loci that result in neurodevelopmental defects of gonadotropic hormone-releasing hormone (GnRH) neuron migration or disrupt neuroendocrine GnRH secretion and action [36]. Human spermatogenesis takes approximately 72 days to be completed [37]. During this

long process, the activation of about 2000 protein-coding genes contributes to the genesis and maturation of millions of male gametes. It is, therefore, clear that the genetic landscape of male infertility is highly complex and research in this field requires specific approaches [38]. Androgenetics has gone through all the classic steps of molecular genetics, starting from Sanger sequencing for *de novo* mutations and finally by Next Generation Sequencing (NGS). The discovery of novel genetic variants associated with male infertility has accelerated rapidly over the past decade, driven by the application of tools for genome-wide discovery, although early GWAS used array-based approaches, next-generation sequencing (NGS) has more recently become the predominant tool for genetic diversity.

Future Directions

Genome-Wide Association Studies (GWAS)

Genome-wide association studies (GWAS) hold promises for identifying novel genetic variants associated with male infertility. By analyzing the entire genome of large cohorts, GWAS can uncover previously unknown genetic factors and provide insights into the complex genetic architecture of male infertility.

Gene Editing Technologies

Gene editing technologies, such as CRISPR-Cas9, offer potential therapeutic interventions for genetic causes of male infertility. By precisely targeting and correcting specific genetic mutations, gene editing could restore normal spermatogenesis and fertility. However, ethical considerations and technical challenges need to be addressed before these therapies can be widely implemented.

Stem Cell Research

Stem cell research is exploring the possibility of generating sperm from pluripotent stem cells. This approach could provide new treatment options for men with non-obstructive azoospermia who lack viable sperm. While still in the experimental stages, stem cell-derived gametes hold promise for future fertility treatments.

CONCLUSION

The genetic basis of male infertility is complex and multifaceted, involving chromosomal abnormalities, single-gene mutations, and Y chromosome microdeletions. Advances in genetic testing and diagnostic technologies have significantly improved our understanding and management of male infertility. Future research in genome-wide association studies, gene editing, and stem cell therapies holds promise for developing novel treatments and improving reproductive outcomes for infertile men. Collaborative efforts between geneticists, urologists, and reproductive specialists are essential for translating these scientific advancements into clinical practice.

ACKNOWLEDGEMENT

We are thankful to Janaki Medical College Teaching Hospital (JMCTH) in Ramdaiya, Dhanusa Dham, Nepal for all the cordial support during this study.

Conflict of interest: None declared

Funding: None

Author's Contribution:
participated in study design write up of the draft and final version of the manuscript-**NT, AS, APG;** involved in study design, write up

and final version of the manuscript-**NT;**participated in correcting the draft and final version of the manuscript-**AS;**participated in correcting the draft and final version of the manuscript**-APG.** All authors contributed to the final version of the manuscript and approved the submission.

REFERENCES

1. Katz DJ, Teloken P, Shoshany O. Male infertility - The other side of the equation. Aust Fam Physician 2017 [cited 2022 Jan 9];46(9):641–6.
2. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 2007 [cited 2022 Jan 9];22(6):1506–12.
3. Krausz C. Male infertility: pathogenesis and clinical diagnosis. Best Pract Res Clin Endocrinol Metab 2011 Apr [cited 2022 Jan 9];25(2):271–85.
4. Krausz C, Riera-Escamilla A. Genetics of male infertility. Nat Rev Urol 2018 Jun;15(6):369–84.
5. Esteves SC, Roque M, Agarwal A. Outcome of assisted reproductive technology in men with treated and untreated varicocele : systematic review and meta - analysis 2016;(July 2015):254–8.
6. Shamsi MB, Kumar K, Dada R. Genetic and epigenetic factors: Role in male infertility. In: Indian Journal of Urology 2011; Jan;27(1):110-20.
7. Dada R, Kumar R, Shamsi MB, Tanwar M, Pathak D, Venkatesh S, et al. Genetic screening in couples experiencing recurrent assisted procreation failure. Indian J Biochem Biophys 2008 Apr [cited 2022 Jan 9];45(2):116–20.
8. Yoshida A, Miura K, Shirai M. Cytogenetic survey of 1,007 infertile males. Urol Int 1997;58(3).
9. Meza-Espinoza JP, Ortiz Anguiano L, Rivera H. Chromosomal abnormalities in couples with reproductive disorders. Gynecol Obstet Invest 2008;66(4).
10. Chandley AC, Maclean N, Edmond P, Fletcher J, Watson GS. Cytogenetics and infertility in man*: II. Testicular histology and meiosis. Ann Hum Genet 1976;40(2).
11. Tiepolo L, Zuffardi O. Localization of factors controlling spermatogenesis in the nonfluorescent portion of the human y chromosome long arm. Hum Genet 1976;34(2).
12. Skaletsky H, Kuroda-Kawaguchl T, Minx PJ, Cordum HS, Hlllier LD, Brown LG, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. Nature 2003 Jun 19 [cited 2022 Jan 9];423(6942):825–37.
13. Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. Hum Mol Genet 1996;5(7).
14. Navarro-Costa P, Gonçalves J, Plancha CE. The AZFc region of the Y chromosome: at the crossroads between genetic diversity and male infertility. Hum Reprod Update 2010 Mar 18 [cited 2022 Jan 9];16(5):525–42.
15. de Llanos M, Ballescà JL, Gázquez C, Margarit E, Oliva R. High frequency of gr/gr chromosome Y deletions in consecutive oligospermic ICSI candidates. Hum Reprod 2005; Jan;20(1):216-20.
16. Dada R, Gupta NP, Kucheria K. Semen cryoconservation in men with AZFc microdeletion. Clin Genet 2003 Jul 1 [cited 2022 Jan 9];64(1):74–5.
17. Sharma N, Singh M, Acharya N, Singh SK, Thapa BR, Kaur G, et al. Implication of the cystic fibrosis transmembrane conductance regulator gene in infertile family members of Indian CF patients. Biochem Genet 2008;46(11–12).
18. Selhub J. Homocysteine metabolism. Annu Rev Nutr 1999 [cited 2022 Jan 10];19:217–46.
19. Zhang Y, Malekpour M, Al-Madani N, Kahrizi K, Zanganeh M, Mohseni M, et al. Sensorineural deafness and male infertility: A contiguous gene deletion syndrome. J Med Genet 2007;44(4).
20. Lyon MF, Hawkes SG. X-linked gene for testicular feminization in the mouse. Nature 1970 [cited 2022 Jan 9];227(5264):1217–9.
21. Brown TR, Lubahn DB, Wilson EM, Joseph DR, French FS, Migeon CJ. Deletion of the steroid-binding domain of the human androgen receptor gene in one family with complete androgen insensitivity syndrome: Evidence for further genetic heterogeneity in this syndrome. Proc Natl Acad Sci USA 1988; Nov;85(21):8151-5.
22. Kerem BS, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989 [cited 2022 Jan

9];245(4922):1073–80.

23. Hutchison CA. DNA sequencing: Bench to bedside and beyond. Nucleic Acids Res 2007; 35(18):6227-37.
24. Miyamoto T, Hasuike S, Yogev L, Maduro MR, Ishikawa M, Westphal H, et al. Azoospermia in patients heterozygous for a mutation in SYCP3. Lancet (London, England) 2003 Nov 22 [cited 2022 Jan 9];362(9397):1714–9.
25. Dieterich K, Soto Rifo R, Karen Faure A, Hennebicq S, Amar B Ben, Zahi M, et al. Homozygous mutation of AURKC yields large-headed polyploid spermatozoa and causes male infertility. Nat Genet 2007;39(5).
26. Harbuz R, Zouari R, Pierre V, Ben Khelifa M, Kharouf M, Coutton C, et al. A recurrent deletion of DPY19L2 causes infertility in man by blocking sperm head elongation and acrosome formation. Am J Hum Genet 2011;88(3).
27. Tüttelmann F, Ruckert C, Röpke A. Disorders of spermatogenesis: Perspectives for novel genetic diagnostics after 20 years of unchanged routine. Medizinische Genet Mitteilungsblatt des Berufsverbandes Medizinische Genet eV 2018 Mar 1 [cited 2022 Jan 10];30(1):12–20.
28. Lopes AM, Aston KI, Thompson E, Carvalho F, Gonçalves J, Huang N, et al. Human spermatogenic failure purges deleterious mutation load from the autosomes and both sex chromosomes, including the gene DMRT1. PLoS Genet 2013 Mar;9(3):e1003349. [cited 2022 Jan 10];9(3).
29. Zhou B, Ho SS, Zhang X, Pattni R, Haraksingh RR, Urban AE. Whole-genome sequencing analysis of CNV using low-coverage and paired-end strategies is efficient and outperforms array-based CNV analysis. J Med Genet 2018;55(11).
30. Ho SS, Urban AE, Mills RE. Structural variation in the sequencing era. Vol. 21, Nature Reviews Genetics 2020; Mar;21(3):171-189.
31. Schilit SLP, Menon S, Friedrich C, Kammin T, Wilch E, Hanscom C, et al. SYCP2 Translocation-Mediated Dysregulation and Frameshift Variants Cause Human Male Infertility. Am J Hum Genet 2020; Jan 2;106(1):41-57.
32. Bamshad MJ, Ng SB, Bigham AW, Tabor HK, Emond MJ, Nickerson DA, et al. Exome sequencing as a tool for Mendelian disease gene discovery. Vol. 12, Nature Reviews Genetics 2011; Sep 27;12(11):745-55.
33. Fernandez-Marmiesse A, Gouveia S, Couce ML. NGS Technologies as a Turning Point in Rare Disease Research , Diagnosis and Treatment. Curr Med Chem 2018 Jul 19 [cited 2022 Jan 9];25(3):404–32.
34. Chertman W, Arora H, Griswold AJ, Lopategui DM, Ramasamy R. Whole Exome Sequencing Identifies a Rare Nonsense Mutation in FAM47C as a Possible Cause of Severe Oligospermia in Brothers With Varicocele. Urology 2019; Jul;129:71-73.
35. Sha YW, Wang X, Xu X, Ding L, Liu WS, Li P, et al. Biallelic mutations in PMFBP1 cause acephalic spermatozoa. Clin Genet 2019;95(2).
36. Cangiano B, Swee DS, Quinton R, Bonomi M. Genetics of congenital hypogonadotropic hypogonadism: peculiarities and phenotype of an oligogenic disease. Hum Genet 2021 Jan 1 [cited 2022 Jan 9];140(1):77–111.
37. Di Persio S, Saracino R, Fera S, Muciaccia B, Esposito V, Boitani C, et al. Spermatogonial kinetics in humans. Development 2017 Oct 1 [cited 2022 Jan 10];144(19):3430–9.
38. Kasak L, Laan M. Monogenic causes of non-obstructive azoospermia: challenges, established knowledge, limitations and perspectives. Vol. 140, Human Genetics 2021; Jan;140(1):135-154.