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Genomics: Tool to predict and prevent male infertility

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1. ABSTRACT

A large number of human diseases arise as a result of genetic abnormalities. With the advent of improved molecular biology techniques, the genetic etiology of male infertility is increasing. The common genetic factors responsible for male infertility are chromosomal abnormalities, Yq microdeletion and cystic fibrosis. These are responsible for approximately 30 percent cases of male infertility. About 40 percent cases of male infertility are categorized as idiopathic. These cases may be associated with genetic and genomic abnormalities. During last few years more and more genes are implicated in male infertility leading to decline in prevalence of idiopathic etiology. In this review we will summarize up to date published works on genetic etiologies of male infertility including our own works. We also briefly describe reproductive technologies used to overcome male infertility, dangers of transmitting genetic disorders to offspring and ways to prevent transmission of genetic disorders during assisted reproduction. At the end we will provide our points on how genomic information can be utilized for prediction and prevention of male infertility in coming years.

2. INTRODUCTION

Infertility is *defined* as the failure to achieve conception even after 12 months of regular unprotected sexual intercourse. Infertility affects approximately 10–15% of couples in their reproductive age (1). Male infertility is as prevalent as female infertility and contributes about 50% cases (2). The incidence of male infertility over the years is rising. Male infertility could result from disorders of hormonal control (pre-testicular) or spermatogenesis (testicular) or sperm transport, epididymal maturation & fertilization (post-testicular). The majority (over 85%) of cases of male infertility are testicular origin. The genetic etiology accounts for up to 30% of cases until recently (3). Still, most cases of male infertility are thought to be idiopathic (4) which may actually be linked to unknown genetic/ genomic abnormalities.

Genetics play important role in the causation of human disease. Genetics affect male infertility by influencing hormonal homeostasis (mostly pre testicular causes), spermatogenesis (testicular causes) and sperm quality & quantity (testicular and post testicular causes). The genetic basis of infertility can result from chromosomal abnormalities, Yq microdeletion/ azoospermia factor (AZF) deletion, copy number variations (CNVs), monogenic, multifactorial, mitochondrial and epigenetic abnormalities. Some of the likely CNV hot spots reported for testis expressed genes are 1p31–33, 6p21, 6p22.1, Xq28, 7q31, 3p21.1, etc (5). Although mitochondrial mutations in sperm decrease sperm motility, in general, it does not impair fertility (6). Epigenetic changes in spermatozoa

are very critical for normal fertilization and embryonic development. Hypermethylation of promoters of genes like MTHFR, PAX8, NTF3, SFN, HRAS, JHM2DA, IGF2, H19, RASGRF1, GTL2, PLAG1, D1RAS3, MEST, KCNQ1, LIT1, SNRPN, etc are implicated with male infertility (7). Monogenic disorders like cystic fibrosis mutation leading to congenital absence of vas deferens (CAVD) can present as obstructive azoospermia. Other abnormalities that could lead to male infertility are sperm chromosome abnormality (8), sperm DNA instability, etc. Infertile male with oligo/ astheno/ teratozoospermia (with normal blood karyotype) have three-fold increase in chromosomal abnormalities in sperms (9).

With the advent of improved molecular biology techniques, the genetic basis of disease is coming up with an increasing number of disorders. This is also observed with male infertility and is soon going to change previous estimates of genetic contribution to male infertility because large number of gene are expressed in the male germ cells and their defect is likely to be responsible for the infertility. It is very important to know underlying genetic etiology as this information can be utilized for identifying abnormality before disease onset, predicting prognosis, preventing disease, planning treatment at/before onset of disease as well as predicting health of the offspring.

Understanding genetics of male infertility depends on the development of research in genomics and epigenomics. Research in this field has resulted accumulation of extensive genomics, epigenomics, transcriptomics and proteomics data. In coming years DNA repositories from informative families will help in defining more and more underlying genetic etiologies thus potential future genetic tests. In this review we will review the known genetic causes of male factor infertility along with some new findings of our group that may be relevant in coming days and futuristic use of genomics as part of predictive & preventive reproductive medicine practice.

3. GENETIC CAUSES OF MALE INFERTILITY

Genetic causes of male infertility are chromosomal abnormalities, AZF deletions of Y chromosome, monogenic disorders, polygenic disorders, multifactorial disorders, mitochondrial or epigenetic disorders. The common causes of male infertility are chromosomal disorders (mostly 47,XXY/ Klinefelter syndrome) and Yq microdeletions/AZF deletions (10,11). Chromosomal abnormalities and Yq microdeletion account for about 25% of cases of male infertility with azoospermia, suggesting that these two abnormalities are very important genetic etiologies of spermatogenic failure. So, it is essential to screen them during evaluation of male infertility (12). The systemic chromosomal disorders are responsible for approximately 5% of male infertility and about 15% in azoospermia (2). The sex chromosome aneuploidy, in particular Klinefelter syndrome (Figure 1), is the most common chromosomal abnormality detected in male infertility (13). It is seen in one out of every 1000 males. The patient is usually tall and presents with small testes, reduced fertility and gynecomastia. About 50% cases of Klinefelter syndrome are mosaic (Figure 2), where 47,XXY cell line is present along with 46,XX or 46,XY or 48,XXYY or 48,XXXY cell lines or any combinations. The sex chromosomes play a major role in germ cell development in mammals as sex chromosomes contain many genes that are expressed in the gonads. The gonadal defect in 47,XXY (Klinefelter syndrome) patient is mainly due to germ cell survival (10) or germ cell maturation breakdown (14).

Other sex chromosome abnormalities seen with male infertility are 46,XX (15,16) sex reversal male (Figure 3), dicentric Y (Figure 4), etc. The XX male syndrome is a rare genetic disorder. The phenotype is variable; ranging from a severe impairment of the external genitalia to a normal male phenotype with infertility. This syndrome was first described by de la Chapelle *et al* (17). The 46,XX male syndrome affects 1 in 20000 newborn males (18). In general, SRY-positive 46,XX male individuals present somehow similar to Klinefelter syndrome including normal external male genitalia, soft small testes, gynecomastia, poor facial hair, diminished libido, hypergonadotropic hypogonadism and low testosterone (Figure 3). Testicular histology or cytology with this syndrome is inconsistent; some shows hyalinization of seminiferous tubule with absence of germ cells while others present with Sertoli cell only syndrome (19).

Dicentric Y (Figure 4) is the most frequent structural rearrangement of the Y chromosome. Often centromeres are close to each other and act as monocentric thus replicate as normal chromosome (20). Often one of the centromeres is functionally inactive (21–23). Dicentric Y with longer inter-centromeric distance relies heavily on functional inactivation of one centromere to achieve mitotic stability. In contrast, those with shorter inter-centromeric distance are less dependent upon this mechanism (24). Mitosis may be possible in somatic cells in this case (with longer inter-centromeric distance) presumably because of the cell survival phenomenon through inactivation of one centromere. But in germ cell meiosis requires pseudo autosomal region (PAR) paring and changes of PAR CNVs associated with dicentric Y will lead to meiotic arrest. Spermatogenic failure is reported in cases of Y chromosome structural abnormalities, including dicentric Y chromosome (25). Undisturbed pairing of sex chromosome is an essential condition of correct segregation of the chromosomes during spermatogenesis (26,27). Chromosomal translocations, in particular autosomal are also observed 4–10 times

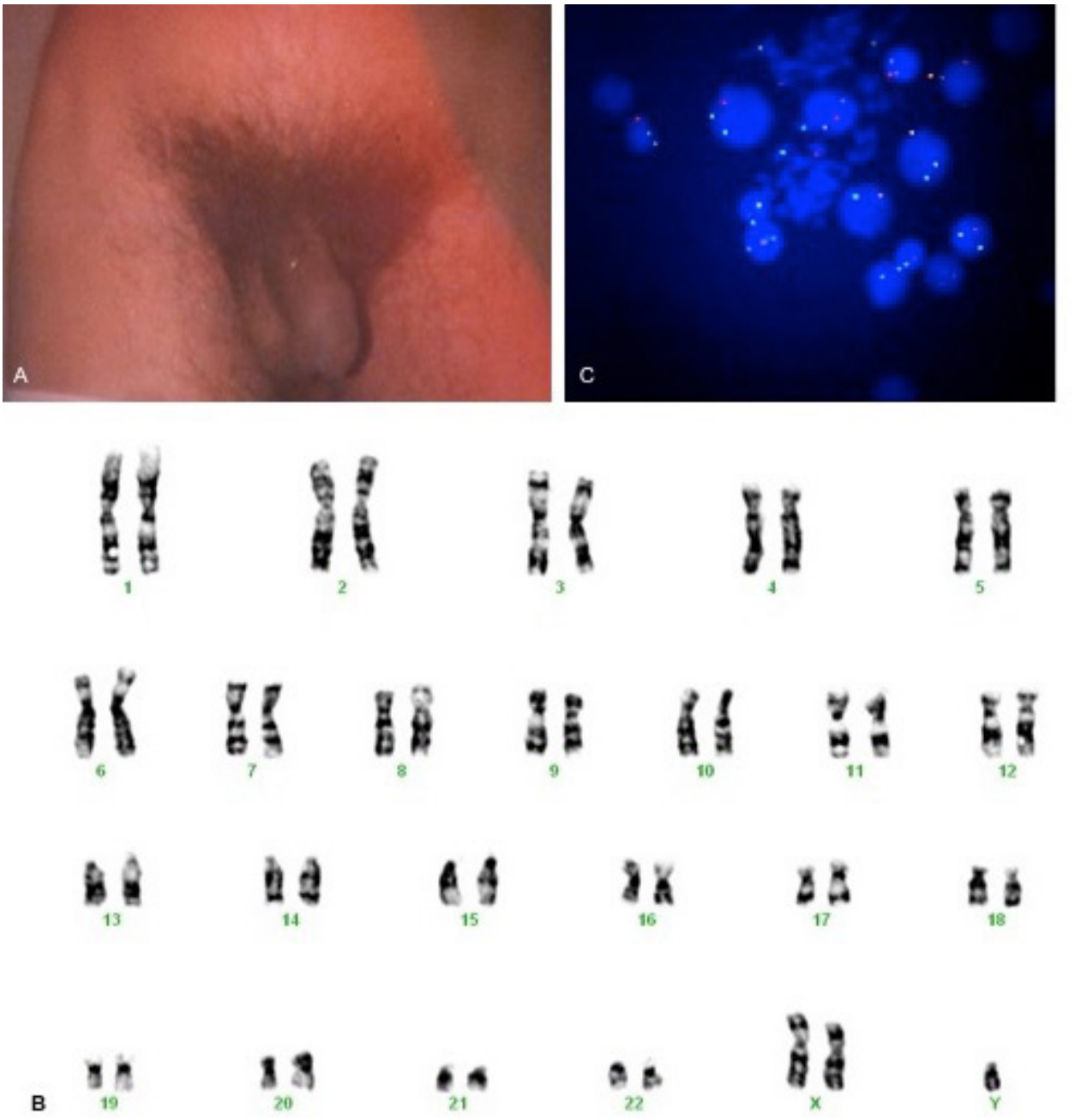

Figure 1. Klinefelter Syndrome. A. External genitalia (normal size penis, small testes & normal pubic hairs). B. Karyogram using Geimsa stain (47,XXY chromosome constitution). C. XY FISH image on metaphase & interphase cells (containing two green/X centromere and one red/Y centromere signals suggesting XXY state i.e., Klinefelter Syndrome/47,XXY).

more frequently in infertile males in comparison with normal fertile male (28). Carriers of translocations usually have a normal phenotype but could be infertile if breakpoints involved genes of spermatogenesis (2). Rarely chromosomal abnormality may restrict only to gonads (gonadal mosaicism) and present as infertility in translocation carriers or recurrent chromosomal abnormality in offspring. Moreover, sperm aneuploidy rate is increased in oligospermia, oligo-azoospermia, asthenozoospermia, etc and sperm aneuploidy test should be employed as a routine screening test before intracytoplasmic sperm injection to assess the need for preimplantation/prenatal genetic diagnosis. Sperm aneuploidy assessment is carried out by fluorescence *in situ* hybridization analysis (FISH) test (Figure 5), as it appears to be valuable and reliable

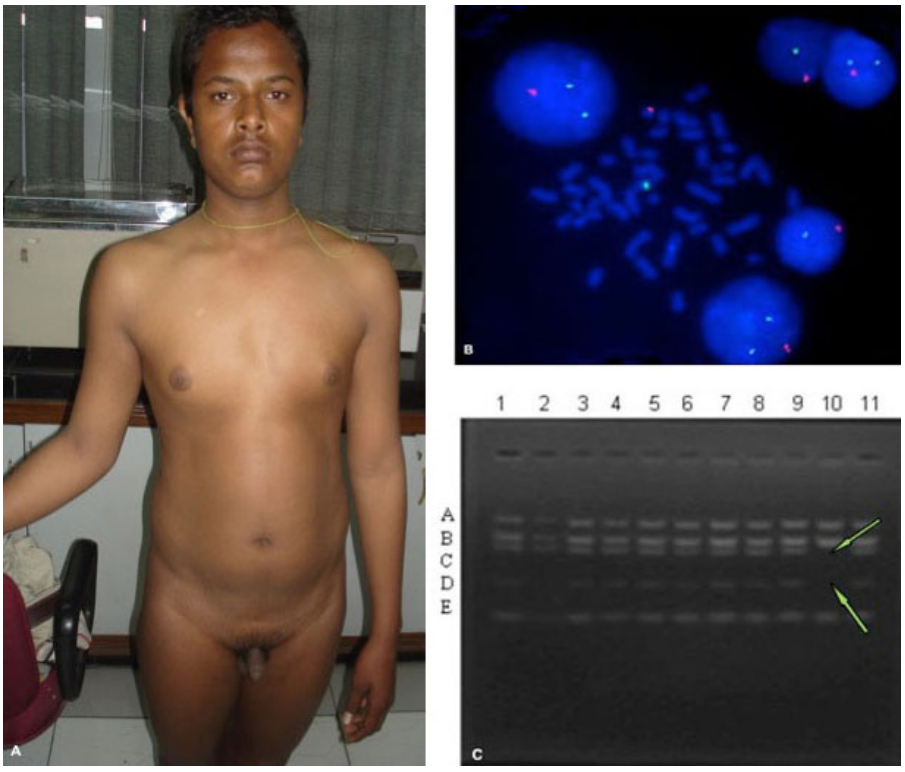

Figure 2. Mosaic Klinefelter syndrome with AZFc deletion. A. Clinical photograph (tall stature, sparse body hairs, sparse moustache, sparse side burn, small testes, gynecomastia but normal penis size and pubic hair). B. XY FISH image (cells containing one green/X centromere and one red/Y centromere signals suggesting XY cells: 1 metaphase and 2 interphase cells and remaining cells with two green/XX and one red/Y signal suggesting XXY cells i.e., mosaic Klinefelter syndrome (XY/XXY). C. AZFc deletion (SY254 & SY255 markers deleted; arrow).

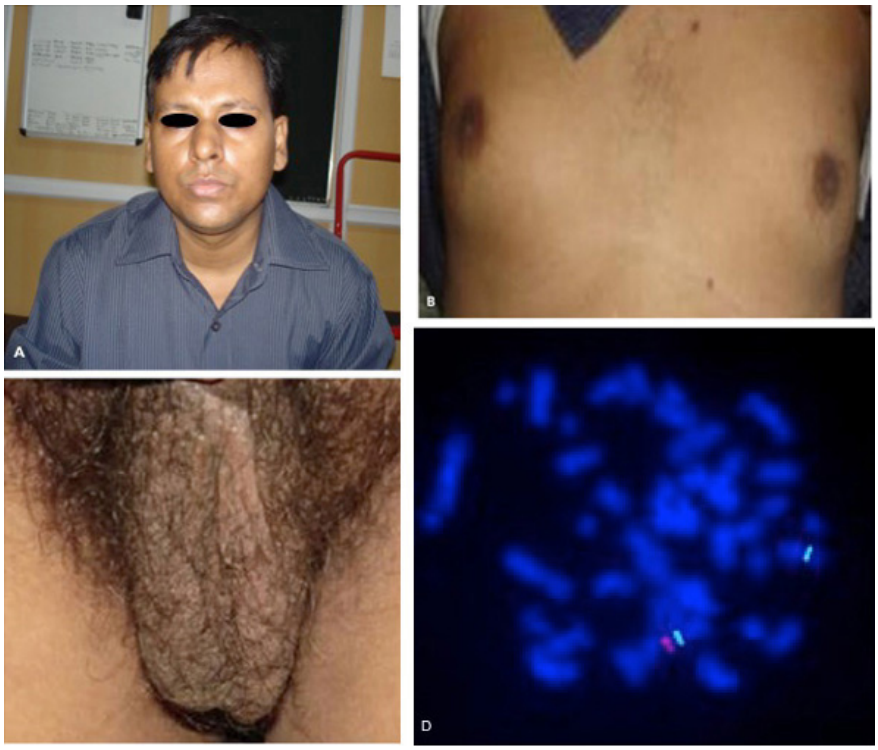

Figure 3. 46,XX (SRY positive) sex reverse male. A. Sparse facial hairs. B. Sparse body hairs and gynecomastia. C. External genitalia (well developed scrotum containing ill defined small testes). D. Metaphase FISH image (X centromere as green, SRY as red & Y centromere as yellow/absent in image. Two green indicates 2 centromeres of X chromosome and one red indicates SRY on Xp terminal. Absence of yellow spot indicates no Y chromosome centromeres).

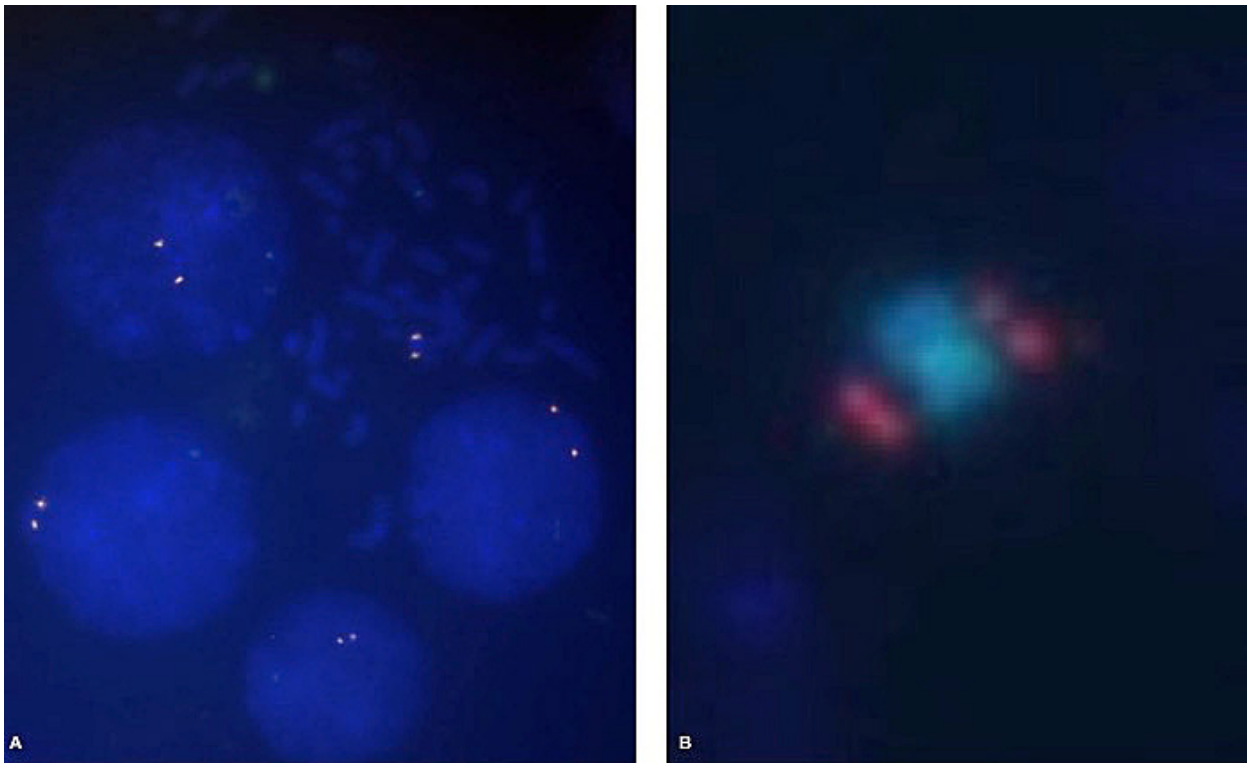

Figure 4. Dicentric Y chromosome. A. FISH images on interphase & metaphase cells (2 centromeres of Y chromosome/red signals). B. FISH images of Y chromosome (greenish intervening area as heterochromatic regions of Y chromosome long arm i.e., Yqh and red as 2 centromeres of Y chromosome).

test to study aneuploidy (8,29). Sperm FISH may be helpful for patients with Klinefelter syndrome, structural chromosomal abnormalities, teratospermia in particular macrocephalic, multinucleated and multiflagellate sperm and 46,XY men with nonobstructive azoospermia (before intra cytoplasmic sperm injection/ICSI with epididymal/testicular sperm aspiration). Sperm FISH in these men will aid in counseling and decision making. Higher incidence of aneuploidies, in particular sex chromosome was observed in embryos derived from *in vitro* fertilization/ IVF & ICSI using epididymal or testicular sperm. Hence it is important to include sperm FISH analysis in preliminary tests for infertile couples with repeated IVF failures (30).

The Y chromosome is very important for male sex determination, differentiation and fertility because it contains many genes critical for development of male gonads and spermatogenesis (Table 1). However, human Y chromosome has limited number of genes as compared to other chromosomes. This may have resulted from degeneration process during evolution (31). The genes on Y chromosome are subdivided into two groups. The first group has genes which are expressed ubiquitously, exist as single copy having X homologues and perform housekeeping functions. The second group includes genes that have multiple copies (except SRY) and testes specific expression performing additional specialized functions. The X homologue genes are important as these provide an alternate answer for gene dose compensation. These genes also escape X inactivation and encode for proteins (32).

Spermatogenesis related genes of Y chromosome are located on Yq11.2 region, known as AZF/azoospermia factor region. AZF deletion or Yq microdeletion is frequently observed with male infertility (Figures 6–8). The prevalence of Yq microdeletion/ AZF deletion in azoospermic men ranges from 10%–15% and in oligozoospermic men from 5%–10% (33). The Yq microdeletion/ AZF deletion (0.8–7.7 mb size) is most common identifiable genetic cause of spermatogenic failure (34,35). Most deletions arise *de novo* indicating unstable nature of the region due to presence of repetitive palindromic DNA sequences (36). Due to high degree of homology between these palindromes intra-chromosomal recombination and rearrangements occur frequently leading to deletions or duplications. AZF genes encode for 27 distinct proteins (37) and have key roles in spermatogenesis, including germ cell cycle regulation and meiosis (38). The AZF is comprised of three sub-regions; AZFa, located on Yq11.21 and AZFb & AZFc, partially overlapping regions, located on Yq11.221 to Yq11.23 (39,40). The size of the AZFa region is over 1Mb whereas of AZFb covers 1–3 Mb and AZFc is about 3.5 Mb. Another

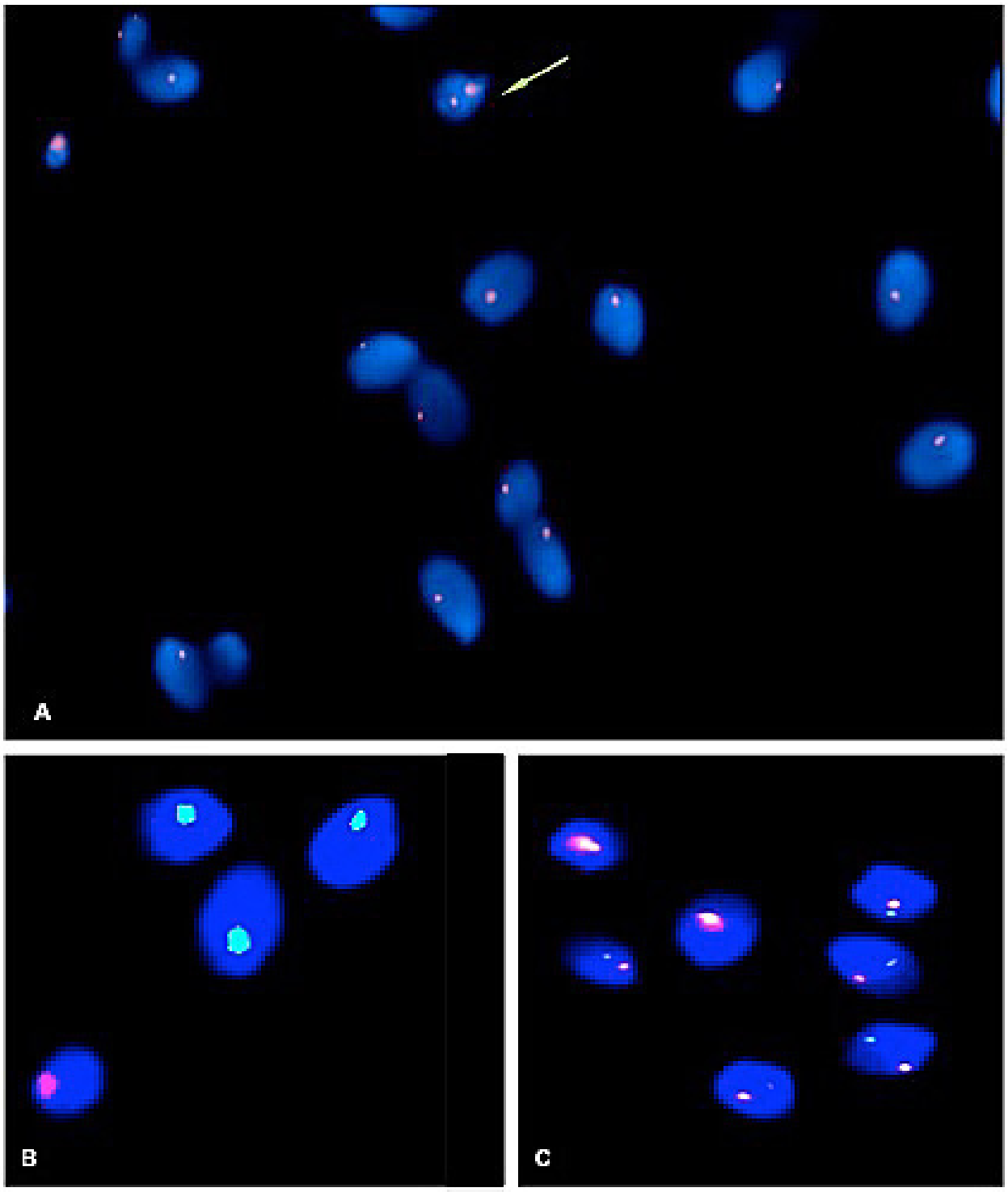

Figure 5. Sperm FISH. A. Chromosome 21 mono probe FISH images (normal/monosomic and abnormal/disomic/arrow). B. XY dual probes FISH images (X/green and Y/red bearing sperms). C. XY1 triple probes FISH (X1/green & yellow and Y1/ red & yellow bearing sperms).

region AZFd is located between AZFb and AZFc, but requires more verification (41). The AZFa region (Yq11.21) contains few genes viz., USP9Y, DDX3Y and UTY (32,42,43). USP9Y (ubiquitin specific protease 9; older name Drosophila fat facets related Y) is situated at genomic coordinate Y:12701230–12860843, exists in a single copy and has an X-homologue, which escapes X-inactivation. USP9Y occupies less than half of the AZFa interval (43). DDX3Y (Dead/H Box 3, Y-Linked; older name DBY) is situated at

Table 1. Human Y chromosome specific genes

Gene	Cytogenetic Location	Pathology/function	References
SRY	Yp11.2	testis-determining factor, initiates male sex determination	156
DAZ1	Yq11.223	important for spermatogenesis; 4 copies	157
DAZ2	Yq11.223	important for spermatogenesis/ non obstructive azoospermia	48
DAZ3	Yq11.23	important for spermatogenesis; 4 copies	158
DAZ4	Yp11.23	important for spermatogenesis; 4 copies	159
HSFY1, HSFY 2	Yq11.222	candidate gene for azoospermia	45
CDY2A	Yq11.222	testis-specific gene family; maturation arrest	45
CDY1	Yq11.23	expressed specifically in testis histone acetyltransferase catalytic domain	159
RBMY1A1	Yq11.223	azoospermia or severe oligospermia; splicing regulator during spermatogenesis	160
TSPY1	Yq11.2	TSPY function is related to spermatogonial proliferation in a phosphorylation-dependent manner; TSPY1 CNV affects susceptibility to spermatogenic failure by modulating the efficiency of spermatogenesis	161,162
BPY2/VCY2	Yq11.223	no expression in spermatocytes and spermatids, in maturation arrest or hypospermatogenesis	163
DDX3Y	Yq11.221	Mutations in this gene result in male infertility, a reduction in germ cell numbers, and can result in Sertoli-cell only syndrome	164
PRY1/PRY2	Yq11.223	no obvious effect, protein coding gene, expressed specifically in testis	32,37,165
TTTY4/TTTY5/ TTTY6/ TTTY17	Yq11.223	does not encode protein; ncRNA	37
TTTY3	Yq11.23	does not encode protein; ncRNA	37
XKRY	Yq11.222	exist in multiple copies on the Y chromosome and are expressed specifically in testis; protein coding	32
CYORF15B	Yq11.2	does not engage in X-Y crossover events	37
CYORF15A/TXLNGY	Yq11.22	does not engage in X-Y crossover events	37
EIF1AY	Yq11.223	essential translation initiation factor; protein coding	32
VCY	Yq11.221	expressed exclusively in male germ cells	32
NLGN4Y	Yq11.221	expressed in fetal and adult brain, prostate, and testis	37
TGIF2LY	Yq11.2	transcriptional role in testis	166
UTY	Yq11.221	may have role in spermatogenesis and a Y-specific growth gene	167
GCY	Yq12	on stature	168
TMSB4Y	Yq11.221	expressed in many tissues and have homologs on the X chromosome that escape X inactivation	32
GOLGA2LY	Yq11.23	does not appear to encode a protein	37
CSPG4LY	Yq11.23	does not appear to encode a protein	37
USP9Y	Yq11.221	Non pathogenic (alone)	73
KDM5D/ SMCY	Yq11.223	may be necessary for normal function	169
PCDH11Y	Yp11.2	male-specific protocadherin that acts through the Wnt signaling pathway	170
TBL1Y	Yp11.2	expressed in fetal brain and prostate	37
AMELY	Yp11.2	amelogenesis imperfecta show lyonization, i.e., a mosaic pattern of enamel abnormality	171
ZFY	Yp11.2	appears to be involved in sperm or testis maturation	172
CSF2RA	Yp11.2 (PAR1)	receptor for colony stimulating factor 2, a cytokine which controls the production, differentiation, and function of granulocytes and macrophages	173
GTPBP6	Yp11.2 (PAR1)	Unknown	174
PPP2R3B	Yp11.2 (PAR1)	Regulates DNA replication. Over-expression causes G1 cell cycle arrest	99
SHOX	Yp11.2 (PAR1)	Transcription factor associated to short stature syndromes	175

CRLF2	Yp11.2 (PAR1)	Receptors that bind TSLP cytokine; enhances dendritic cell maturation and $CD4^+$ T cell proliferation	176
CSFR2Rα	Yp11.2 (PAR1)	Receptor that binds granulocyte-macrophage colony-stimulating factor (GM-CSF); regulate eosinophil and macrophage development	177
IL3RA	Yp11.2 (PAR1)	Receptors for interleukin 3	178
SLC25A6	Yp11.2 (PAR1)	Member of the ADP/ATP translocase family, role in Th cell survival and immune cell homeostasis	179
P2RY8	Yp11.2 (PAR1)	Member of the purine nucleotide g-protein coupled receptor gene	180
CXYorf3	Yp11.2 (PAR1)	Alternative splicing regulator	181
ASMT	Yp11.2 (PAR1)	Catalyses final reaction in melatonin synthesis	182
DHRSXY	Yp11.2 (PAR1)	Encodes an oxidoreductase of the short-chain dehydrogenase/ reductase family	183
ZBED1	Yp11.2. (PAR1)	Transposition of other transposable elements	184
CD99	Yp11.2 (PAR1)	Cell surface molecule involved in T-cell adhesion and activation of death pathway in T-cell	185
XGR	Yp11.2 (PAR1)	Regulates the expression of MIC2 and XG	186
RPS4Y1	Yp11.2	Encode isoforms of ribosomal protein S4	187
PRKY	Yp11.2	Unknown	188
VAMP7	Yq12	Protein coding	189
WASH6P/CXYORF1	Yq12	Pseudogene	190

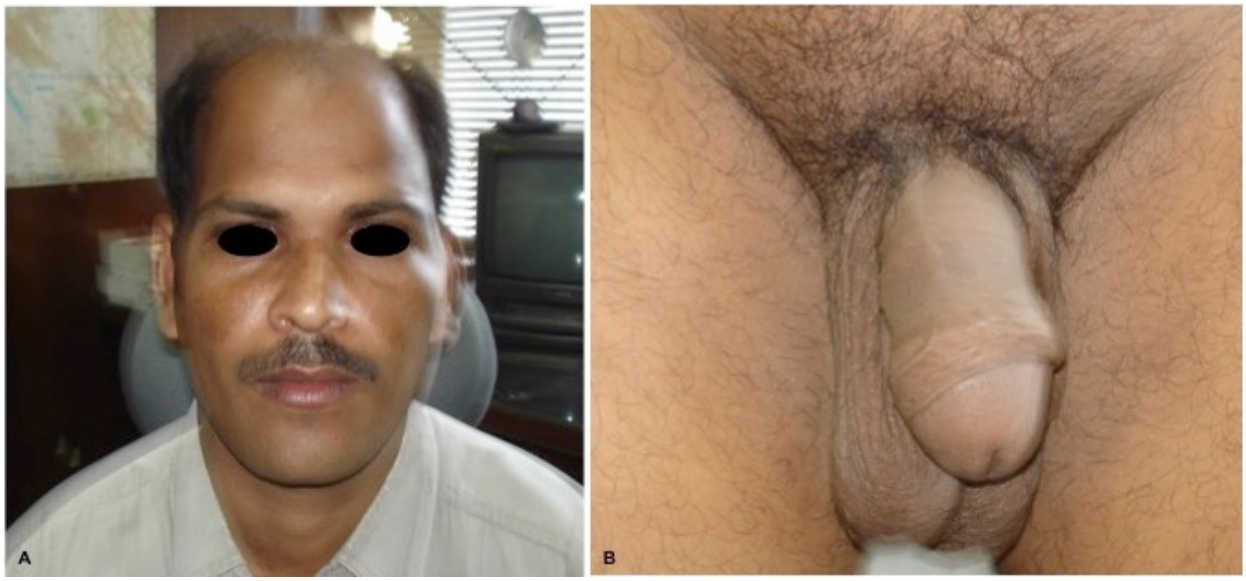

Figure 6. AZFab deletion case. A. Facial profile (normal virilization). B. External genitalia (normal appearance).

genomic coordinate Y:12903998–12920477, has an X-homologue (DDX3X) on the short arm of the X chromosome and is associated with Sertoli cell-only syndrome or hypospermatogenesis. UTY (ubiquitous TPR motif on the Y) is situated at genomic coordinate Y:13230769–13480669, has an X homologue and is not directly involved with male infertility. Deletion of a single gene (eg, DBY/DDX3Y) or combinations of genes has been associated with spermatogenic disruption, in particular with sertoli cell only syndrome (39) or hypospermatogenesis (43). The AZFb region (Yq11.221-q11.223) contains many genes like CDY2A, CDY2B, PRORY/CYorf17, EIF1AY, HSFY1, HSFY2, PRY, RBMY1A1, RBMY1B, RBMY1D, RBMY1E, RBMY1F, RBMY1J and RPS4Y2. The role of AZFb loss in male infertility can be explained by the involvement of HSFY1 and HSFY2 (heat shock transcription factor, Y-linked 1 and 2) genes. These genes have testis-specific expression and contribute in spermatocyte maturation (44). Deletion or under expression of HSFY is associated with testicular maturation arrest (45,46). RBMY genes are expressed only in the testicular germ cells (47). The AZFc region contains several genes like CDY1B, CYorf17, EIFIAY, PRY, PRY2, RBMY1A1,

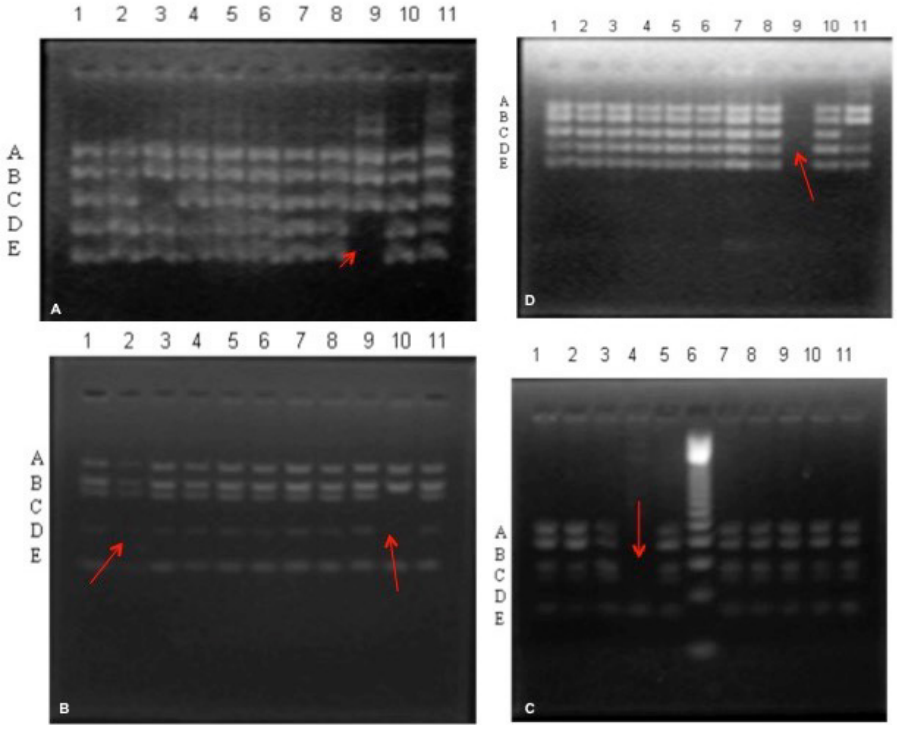

Figure 7. Agarose gel electrophorogram images of AZF deletions. A. AZFa deletion (marker SY86 & SY84 deleted) B. AZFb deletion (marker SY134 deleted). C. AZFc deletion (marker SY242 & SY208 deleted). D. AZFbc overlapping region deletion (markers SY128, SY121, SY145 of AZFb region & SY255 of AZFc region deleted).

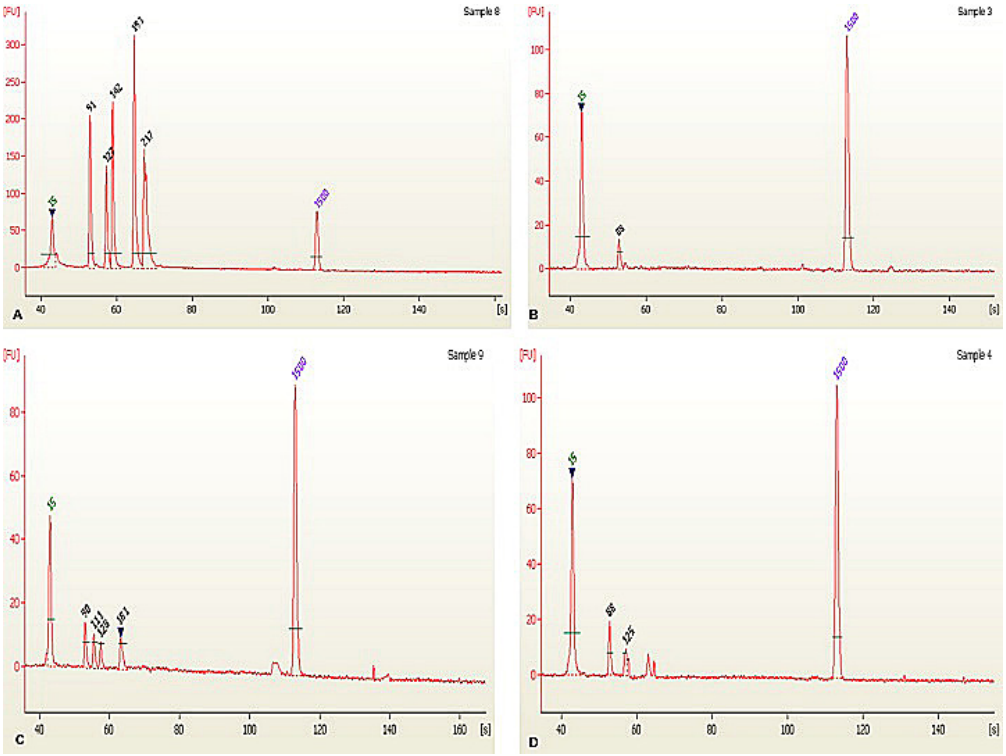

Figure 8. Microcapillary electrophorogram images of AZF deletions. A. PCR amplification using multiplex C containing SMCX(83), SY255(124), SY145(143), SY121(190) and SY128(228) markers panel in normal control. B. PCR amplification using multiplex C markers panel in patient. C. PCR amplification using multiplex D containing SMCX(83), SY124(109), SY152(125) and SY133(177) markers panel in normal control. D. PCR amplification using multiplex D markers panel in patient (size in bp is shown in braket).

RBMY1B, RBMY1D, RBMY1E, RBMY1F, RBMY1J, RPS4Y2, BPY2, BPY2B, DAZ1, DAZ2, DAZ3, KDM5D, TTTY3, TTTY4, TTTY6, TTTY17, TSPY1, CSPG4LY, GOLGA2LY, etc. The Yq11.222-q11.223 (AZFbc) has multiple genes like CYorf17 (PRORY), EIF1AY, HSFY2, KDM5D, RPS4Y2, PRY, PRY2 and RBMY family genes (all 6 copies). These are important for spermatogenesis (Gene, GeneCards, OMIM, etc databases). Similarly, Yq11.223 (AZFc) contains PRY, PRY2 and RBMY family genes (6 copies), Yq11.223-q11.23 (AZFc) contains CDY1B gene and Yq11.23 (AZFc) contains CDY1 gene. These genes are important for the spermatogenesis (Gene, GeneCards, Online Mendelian Inheritance in Man/OMIM, etc databases). One of the important genes in AZFc region is DAZ and this gene belongs to a multigene family. Several copies of DAZ gene (with individual variation in copy number) are present in AZFc region (39,48). The gene has structural similarity with RBMY. It is a 42 kb gene comprising 16 exons. Deletion of this gene is associated with spermatogenic defects (49). The AZF region is one of the unstable spot in human genome. The Y chromosome has a unique structure, covered by large palindromes of long, near identical repeats (37). This makes the Y chromosome prone to undergo rearrangements, especially in AZFc region (36) and thus AZF deletion is the leading genetic causes of spermatogenic failure.

The reasons for disruption in spermatogenesis beyond chromosome abnormalities, AZF deletions and CFTR mutations (responsible for congenital bilateral agenesis of vas deference i.e., obstructive azoospermia) remain largely unclear until recently. After full clinical workup, about 30% cases with male infertility are considered idiopathic and an additional 40% have insufficient/uncertain causes (50). On the other hand, it is estimated that about 30% of azoospermia or oligozoospermia are caused by chromosomal abnormalities or mutations or disruption of genes involved in germ cell production and function (51). A large number of genes (approximately 1 in 25 of all mammalian genes) are expressed in the male germline (52) and mutations in these genes could cause male infertility. Mutations of genes that regulate recombination and repair of the genome can lead to meiotic arrest (53). Androgens are required for spermatogenesis and its activity is mediated by the androgen receptor. Androgen receptor variants with resistance to androgen are known to compromise spermatogenesis. Androgen receptor gene also has two trinucleotide (CAG & GGC) polymorphisms with variation in repeat length in the population. The usual range in repeat length of CAG is 9 to 36 repeats (54). Individuals with more than 40 repeats present with reduced virilization, defective spermatogenesis and infertility (55).

Mitochondrial DNA is inherited maternally and found in multiple copies in a cell. Mutated & wild type mitochondrial DNA mixture (heteroplasmy) in varying frequency is observed within cells. Mitochondrial DNA produces disease phenotype if load of the mutated DNA cross a certain threshold, usually over 80%. Mitochondrial DNA (mtDNA) abnormality may influence male fertility, but it is controversial. Abnormal mitochondria can present as defect in sperm motility (56) or sperm dysfunction. During spermiogenesis most cytoplasm and mitochondria are lost and the remaining mitochondria are concentrated around the sperm mid-piece where they are likely to be vital for sperm motility and therefore male fertility. Mitochondrial genes which undergo mutations associated with male infertility are ANT4 (adenine nucleotide transferase 4), IMMPL2 (inner mitochondrial membrane peptidase 2 like), POLG (DNA polymerase subunit gamma), CLPP (caseinolytic mitochondrial matrix peptidase proteolytic subunit), TWNK (twinkle mtDNA helicase), HARS2 (histidyl-tRNA synthetase 2), LARS2 (leucyl-tRNA synthetase 2), AARS2 (alanyl-tRNA synthetase 2), ATPase 6/ATPase 8, TYMP (thymidine phosphorylase), RRMB2 (ribonucleotide reductase regulatory TP53 inducible subunit M2B), etc (57). POLG is involved in the replication of mtDNA. Variations in the CAG repeat numbers of the catalytic subunit of the POLG gene is implicated with male infertility. The ten CAG repeats were found to be the most common allele and absence of these repeats is associated with male infertility (57). However, POLG-CAG repeats variation is not associated with male infertility in Indian population (58).

3.1. Testicular failure

Spermatogenesis is a process of germ cell development and differentiation in seminiferous tubules of the testis. It is characterized by three specific phases: mitosis, meiosis and differentiation involving spermatogonia, spermatocytes and spermatids. Spermatogenesis failure may be primarily due to defect in testes, mostly genetic defects (Table 2) or secondary to acquired pathology. The acquired causes are chemotherapy, radiotherapy, gonadotoxic drugs, vitamin A/zinc deficiencies, chronic liver/kidney failure, infections, endocrinopathy, etc. Other causes are varicocele, cryptorchidism, etc.

Primary testicular failure is a condition where testes fail to produce sperm despite adequate hormonal support and is characterized by high level of gonadotropins, in particular FSH. Primary testicular failure is a major cause of non-obstructive azoospermia and oligospermia. It affects approximately 1% of all men and 10% of those seeking fertility evaluations (59). Primary testicular failure is characterized by interruption of germ cell development and differentiation. There is either an absence of germ cells in testes or presence of germ cells (few or normal numbers) but differentiation

Table 2. Testicular genetic causes of male infertility

Name	Cytogenetic loci	Gene	Defect	Clinical Features	References
Spermatogenic failure 1	Heterogenous	NK	AR	Meiotic arrest at spermatocytes	191
Spermatogenic failure 2	1q21	NK	deletion	Azoospermia	192
Spermatogenic failure 3	6p21.31	SLC26A8	AD	Asthenozoospermia	193
Spermatogenic failure 4	12q23.2	SYCP3	AD	Azoospermia (meiotic arrest)	194
Spermatogenic failure 5	19q13.43	AURKC	AR	Large-headed, multiflagellar, polyploid spermatozoa	195
Spermatogenic failure 6	3q26.31	SPATA16	AR	Globozoospermia (round-headed spermatozoa)	196
Spermatogenic failure 7	11q13.1	CATSPER1	AR	Nonmotile, low count, abnormal sperm	197
Spermatogenic failure 8	9q33.3	NR5A1	AR	Severe spermatogenic failure	198
Spermatogenic failure 9	12q14.2	DPY19L2	AR	Round-headed spermatozoa without an acrosome	199,200
Spermatogenic failure 10	16p13.3	SEPT12	AD	Asthenoteratozoospermia	201
Spermatogenic failure 11	17q21.2	KLHL10	AD	Oligozoospermia, teratozoospermia asynchronous spermatid maturation, degeneration of late spermatids, and marked reduction in the number of late spermatids	202
Spermatogenic failure 12	10q26.11	NANOS1	AD	Severe oligoasthenoteratozoospermia	203
Spermatogenic failure 13	18q11.2	TAF4B	AR	Azoospermia	204
Spermatogenic failure 14	17p13.2	ZMYND15	AR	Maturation arrest in the spermatid stage	204
Spermatogenic failure 15	10q26.3	SYCE1	AR	Arrest at primary spermatocyte stage	205
Spermatogenic failure, XL-1	Xq26.2	USP26	XL	Sertoli cell-only (SCO) syndrome	191
Spermatogenic failure, XL-2	Xq13.1	TEX11	X-LR	Desynapsis, lack of chiasmata and degeneration of spermatocytes during the first meiotic division	206
Spermatogenic failure, YL-1	Yq11	AZFa deleUSP9Y, DBY, UTY	YL	Sertoli Cell-Only Syndrome, Type I	167
Spermatogenic failure, YL-2	Yq11.221	USP9Y	YL	Spermatogenic failure, oligozoospermia or azoospermia	167,207
Chromodomain protein, Y	Yq11.23	CDY1&CDY1B	YL	CDY1a associated with male infertility; DNA-packaging problem	208
Chromodomain protein, Y	Yq11.222	CDY2A & CDY2B	YL	DNA-packaging problem; maturation arrest	45
Heat shock factor Y linked 1	Yq11.222	HSFY1	YL	Azoospermia; maturation arrest	45
Basic Protein, Y chromosome, 2	Yq11.223	BPY2	YL	Severe oligozoospermia or azoospermia	209
Testis-Specific Protein, Y-Linked, 1	Yp11.2	TSPY	YL	Lower sperm production and an elevated risk of spermatogenic failure were observed in males with fewer than 21 TSPY1 copies and in those with more than 55 copies, compared to men with 21 to 55 copies; signaling spermatogonia to enter meiosis; more copies were found in infertile	162,210
Deleted in Azoospermia 1	Yq11.223	DAZ1	YL	non obstructive azoospermia	48
Deleted in Azoospermia 2	Yq11.223	DAZ2	YL	Non obstructive azoospermia	48
Deleted in Azoospermia 3	Yq11.23	DAZ3	YL	Non obstructive azoospermia	48
Deleted in Azoospermia 4	Yq11.223	DAZ4	YL	Sertoli cell-only syndrome or maturation arrest	48
Rna-Binding Motif Protein 1	Yq11.223	RBMY1A1	YL	Azoospermia or severe oligospermia	160
Moyamoya disease 4	Xq28/Yq12 (PAR 2)	Deletion including IL9R	XLR	Short stature, hypergonadotropic hypogonadism and facial dysmorphism	211

Adrenal hypoplasia, congenital	Xp21.2	NR0B1/DAX1	XL	Lack of Ahch caused progressive degeneration of the testicular germinal epithelium independent of abnormalities in gonadotropin and testosterone production and resulted in male sterility	212
Androgen insensitivity, partial	Xq12	AR	XLR	Severe oligospermia or azoospermiahigh LH & T	213
Spinal and bulbar muscular atrophy of Kennedy	Xq12	AR	XLR	Male infertility associated with impaired spermatogenesis	214
TATA-box binding protein associated factor 7 like	Xq22.1	TAF7L	AR	Testis-specific expression, spermatogenesis-specific component of the DNA-binding, possible contributor to infertility in men; involved in spermatogenesis	215
46XX sex reversal 3	Xq26.3	SOX3-RELATED	XLD	Loss of normal spermatogenesis, thickening and hyalinization of the tubular basal lamina, and diminished numbers of interstitial cells	216
Chromosome Xq27.3-q28 duplication syndrome	Xq27.3-q28	at least 28 genes, including FMR1	XLR	Mild mental retardation, mild facial dysmorphism, short stature, and primary testicular failure (high-pitched voice, sparse body hair, abdominal obesity and small testes)	217
Synaptonemal Complex Protein 1	1p13.2	Sycp1	AR	Spermatocytes arrested in pachynema	218
mut S homolog 4	1p31.1	MSH4	AR	Meiosis-specific protein required for reciprocal recombination and proper segregation of homologous chromosomes at meiosis I	219
Bone morphogentic protein 8b	1p34.3	Bmp8b	AR	Infertile due to defective primordial germ cell formation	220
Tektin T, Testicular	1p34.3	TEKT2	AR	Infertility, frequent bending of the sperm flagella and marked defects in motility	221
Cardiomyopathy, Dilated, with Hypergonadotropic Hypogonadism	1q22	LMNA	AD	hypoplastic genitalia and cardiomyopathy, very small testes, primary testicular failure	222
Glyceronephosphate o-acyltransferase	1q42.2	GNPAT	AR	Male infertility, defects in eye development, cataract and optic nerve hypoplasia	223
Olfactory Receptor, Family 2, Subfamily W, Member 3	1q44	OR2W3	AR	Azoospermia and oligozoospermia	224
Leydig cell hypoplasia with hypergonadotropic hypogonadism Type II	2p16.3	LHCGR	AR	Micropenis to severe hypospadius, male hypogonadism	225
Neuronal Pas Domain Protein 2	2q11.2	NPAS2		Infertility, azoospermia, with small testes, elevated FSH levels, and testosterone in the normal range	226
BOLL	2q33.1	BOLL		Germ cell development; meiotic arrest	227
Sperm-Associated Antigen 16	2q34	SPAG16	AD	Impaired spermatogenesis with significant disorganization of sperm axoneme structure	228
Primary ciliary dyskinesia-22	3p21.31	ZMYND10	AR	Chronic cough, sinusitis, bronchiectasis, and male infertility	229
MutL homolog 1	3p22.2	MLH1	AR	Meiotic arrest	230
Deleted in Azoospermia-Like	3p24.3	DAZL	AR	primary spermatogenic defect, arrest at spermatogonia	231
Nuclear Receptor Subfamily 2, Group C, Member 2	3p25.1	Nr2c2	AR	Delayed spermatogenesis and decreased sperm production	232
Microrchidia	3q13.13	MORC1	AR	Arrest of spermatogenesis at an early stage, specifically at the primary to secondary spermatocyte transition	233
Myotonic dystrophy 2 (trinucleotide expansion disorder)	3q21.3	ZNF9	AD	Muscle pain and stiffness, progressive muscle weakness, myotonia, male hypogonadism, cardiac arrhythmias, diabetes, and early cataracts	234
Chloride Channel 2	3q27.1	CLCN2	AR	Germ cells fail to complete meiosis, few primary spermatocytes and spermatogonia	235

Morbid obesity and spermatogenic failure	3q29	CEP19	AR	Obese, hyperphagic, glucose intolerant, insulin resistant and infertile	236
Epidermal growth factor	4q25	EGF	High/ low exp	Oligospermia, hypospermatogenesis	237
Adenosine Deaminase Domain-Containing Protein 1, Testis-Specific	4q27	ADAD1	AR	Retention of differentiated spermatids in seminiferous tubules, and the majority of epididymal sperm had abnormal appearance	238
PR Domain-Containing Protein 9	5p14.2	PRDM9	AR	Sterility due to deficient pairing of homologous chromosomes and impaired sex body formation	239
DEAD-box helicase 4	5q11.2	DDX4/VASA	AR	Spermatogenesis, germ cell development problem	240
Calmodulin-dependent protein kinase IV	5q22.1	CAMK4	AR	Infertile with impairment of spermiogenesis in late elongating spermatids	241
UBE2B male infertility	5q31.1	RAD6B/UBE2B	AR	Male infertility	242
FOXI1	5q35.1	FOXI1	AR	Male infertility and distal renal tubular acidosis	243
mutS homolog 5	6p21.33	MSH5	AR	Meiosis-specific protein required for reciprocal recombination and proper segregation of homologous chromosomes at meiosis I	219
Mediator of DNA damage check point protein 1	6p21.33	MDC1	AR	Growth retardation, male infertility, immune defects, chromosome instability, DNA repair defects and radiation sensitivity	244
Tata Box binding Protein-Like protein1	6q23.2	TBPL1	AR	Sterile due to a late, complete arrest of spermiogenesis	245
Poly (A) Polymerase, Testis-specific	7p22.1	PAPOLB	AR	Arrest of spermiogenesis	246
Mismatch Repair Gene Pmsl 2	7p22.1	PMS2	AR	Infertile, producing only abnormal spermatozoa; abnormalities in chromosome synapsisin meiosis	247
Fk506-binding protein 6	7q11.23	Fkbp6	AR	Sterile male ‘aspermia’	248
Stromal antigen 3	7q22.1	STAG3	AR	Arrest at zygotene-like stage and leads to infertility very strong candidate; gene of non-obstructive oligo/azoospermia in humans	249
Spinocerebellar ataxia 32	7q32-q33	SCA32	AD	Affected males infertile and azoospermic with testicular atrophy,testicular biopsy show complete absence of germ cells & progenitors	250
solute carrier family 4 member 2	7q36.1	Slc4a2	AR	Complete absence of spermatozoa in the seminiferous tubules; interruption in spermiogenesis	251
Piwi-Like 2	8p21.3	PIWIL2	Silen-cing	Spermatogenic failure and sterility	252
Regulator of G Protein Signaling 22	8q22.2	RGS22	NK	Defective sperm development	253
Primary ciliary Dyskinesia, 1	9p13.3	DNAI1	AR	Immotile spermatozoa, with the sperm tail appearing straight and stiff	254
DnaJ (Hsp40) homolog, subfamily A, member 1	9p21.1	Dnaja1	AR	Primary defect of Sertoli cells in maintaining spermiogenesis; disruption of Sertoli-germ cell adherens junctions	255
Doublesex & MAB3 -related transcript factor 1	9p24.3	DMRT1	AR	Severe testis hypoplasia Sertoli cells failed to differentiate, and germ cells were missing, apparently due to premeiotic germ cell death	256
CDC28 protein kinase regulatory subunit 2	9q22.2	Cks2	AR	Male germ cells arrest at anaphase I, Failure of germ cells to progress past the first meiotic metaphase	257
Pseudohermaphroditism, male, with gynecomastia	9q22.32	HSD17B3	AR	Female to male at puberty	258
cAMP responsive element modulator	10p11.21	CREM		Defective spermiogenesis postmeiotic arrest at the first step of spermiogenesis, Late spermatid absent	259
Sperm-Associated Antigen 6	10p12.2	SPAG6	AR	Sperm motility defects and morphologic abnormalities, with frequent loss of the sperm head and disorganized flagellar structures, including loss of central pair of microtubule	260

Cleavage stimulation factor, 3-prime pre-rna, subunit 2, 64-kd, tau variant	10q21.1	CSTF2T	AR	Infertile, aberrant spermatogenesis, resemble oligoasthenoteratozoospermia	261
Deleted in primary ciliary dyskinesia	10q24.32	DPCD	AR	Features of primary ciliary dyskinesia	262
Polymerase, DNA, lambda	10q24.32	POLL	AR	Hydrocephalus, high mortality rate after birth, situs inversus totalis, chronic sinusitis and male infertility due to immotility of sperm	262
RNA-Binding Motif Protein, X Chr, Like 2	11p15.4	RBMXL2	NK	Infertile, with low sperm counts, degenerate seminiferous tubules, and abnormal sperm morphology	263
Zinc Finger- and BTB Domain-Containing Prot. 16	11q23.2	ZBTB16	AR	Skeletal defects, genital hypoplasia, and mental retardation	264
H2AX histone	11q23.3	H2AFX	AR	Infertile, h2ax-null mouse spermatocytes fail to form a sex body and fail to undergo sex chromosome inactivation	265
Dead Box Polypeptide 25	11q24.2	DDX25	AR	Grth -/- male mice exhibit normal sexual behaviour, normal gonadotropin and androgen profiles, but sterile. Sterility associated with azoospermia caused by complete arrest of spermiogenesis	266
FKBP4	12p13.33	FKBP4	AR	Infertile	267
Desert hedgehog	12q13.12	Dhh	AR	Dhh-null mice sterile, fails to produce mature spermatozoa, partial gonadal dysgenesis	268,269
Synaptonemal Complex Protein 3	12q23.2	Sycp3	AR	Sterile due to massive apoptotic cell death during meiotic prophase	270
Reed-Sternberg Microtubule-Associated Protein	12q24.31	Rsn	AR	Role in spermatogenesis, Abnormal head morphology	271
Piwi-Like 1	12q24.33	PIWIL1	AR	Spermatogenesis uniformly arrested at the round spermatid stage	272
Ring finger protein 17	13q12.12	RNF17	AR	Arrest as round spermatids	273
Cyclin A1	13q13.3	Ccna1	AR	Block in spermatogenesis before the first meiotic division	274
BCL2-like 2	14q11.2	BCL2L	AR	Late meiotic arrest; apoptosis regulator, loss of germ cells, sterility associated with progressive testicular degeneration	275
serine/threonine/tyrosine interacting protein	14q22.1	STYX	AR	Involved in spermiogenesis; defects in round and elongating spermatid development	276
Heat-Shock 70-KD Protein 2	14q23.3	HSPA2	AR	Lack postmeiotic spermatids and mature sperm	277
mutL homolog 3	14q24.3	MLH3	AR	Null mice sterile, spermatocytes reached metaphase before succumbing to apoptosis	278
BUB1 mitotic checkpoint serine/ threonine kinase B	15q15.1	BUB1B	AD	Early onset of aging-associated phenotypes and infertility in mice; oligzoospermia	279
Deafness and male infertility syndrome	15q15.3	STRC &CATSPER2	AR	Asthenoteratozoospermia	280
Creatine kinase, mitochondrial 1	15q15.3	CKMT1A		Sensorineural deafness and male infertility	281
aromatase	15q21.2	Cyp19A1	AR	Spermatogenesis arrested at spermiogenic stage	282
cytoplasmic polyadenylation element binding protein 1	15q25.2	Cpeb	AR	Germ cells arrested at pachytene, Defect in homologous chromosome adhesion or synapsis	283
Small Nuclear Ribonucleo-protein Polypeptide A prime	15q26.3	SNRPA1	deletion	Spermatogonia that failed to differentiate into spermatocytes and mature sperm	284
Sperm Protamine P1	16p13.1.3	PRM1	AR	Postmeiotic chromatin condensation defects	285
Katanin, P80 subunit, B1	16q21	KATNB1	AR	Failure of spermiation	286
Spermatid Maturation Protein 1	17p13.1	SPEM1	AR	Sperms deformed, heads bent back (tips of the heads pointed toward the tips of the tails), motility problem	287

P2X1 receptors	17p13.2	P2RX1	AR	Essential for normal male reproductive function	288
Cryptorchidism	19p13.11	INSL3	AD	Cryptorchidism; Increases risk for testicular tumors	289
Nanos, drosophila, homolog, 3	19p13.12	NANOS3		Azoospermia to oligospermia	290
Basigin	19p13.3	BSG	AR	Azoospermia, arrest at meiosis I	291
Immunoglobulin Superfamily, Member 4C	19q13.31	CADM4	AR	Sterility due to disruption of Sertoli/germ cell interactions	292
nanos C2HC-type zinc finger 2	19q13.32	NANOS2/ NANOS3	AR	Defect in spermatogenesis, no germ cells	293
Myotonic dystrophy 1 (trinucleotide expansion disorder)	19q13.32	DMPK	AD	Myotonia, muscular dystrophy, cataracts, hypogonadism, frontal balding and ECG changes	294
BCL2 associated X, apoptosis regulator	19q13.33	Bax	AR	Premeiotic germ cells, but no mature haploid sperm	295
Warburg micro syndrome 4	20p13	TBC1D20	AR	Infertility, spermatogenesis appeared to stop after formation of the spermatid	296
initiator of meiotic double stranded breaks SPATA43	20q13.31	Spo11	AR	Facilitates homolog pairing and promotes synapsis initiation; defects in meiosis; Spermatocytes arrested prior to pachytene with little/no synapsis & undergo apoptosis	297
Disrupted meiotic cDNA 1	22q13.1	DMC1	AR	Arrested in the early zygotene stage and then undergo apoptosis	53
Protein Interacting with C Kinase 1	22q13.1	PICK1	AR	Globozoospermia, fragmentation of acrosomes	298
MEI1	22q13.2	MEI1		Infertile, meiotic arrest caused by defects in chromosome synapsis	299
MOV10-LIKE 1	22q13.33	MOV10L1	AR	Reduced testis size due to meiotic arrest before the pachytene stage	300
Acrosin	22q13.33	ACR	AR	Infertility due to acrosin deficiency	301
Cerebellar Ataxia & Hypergonadotropic Hypogonadism	NK	NK	AR	Cerebellar ataxia and hypogonadotropic hypogonadism	302
Richards-Rundle Syndrome	NK	NK	AR	Mental retardation, underdevelopment of secondary sex characteristics, deafness, ataxia, peripheral muscle wasting and spermatogenic arrest	303
Hypergonadotropic Hypogonadism and Partial Alopecia	NK	NK	AR	Hypergonadotropic hypogonadism and partial alopecia, germinal cell aplasia	304

into spermatozoa is interrupted or germ cells die prematurely. Most primary testicular failure cases present with hypergonadotropic hypogonadism. Primary testicular failure is classified into four distinct subtypes according to histopathology/ cytology viz., Sertoli Cell Only Syndrome, Maturation Arrest, Hypospermatogenesis and Testicular atrophy (Figure 9). Sertoli Cell Only Syndrome (Del Castillo Syndrome/germ cell aplasia) is characterized by male infertility without sexual abnormality. Only sertoli cells line the seminiferous tubules in testes and germ cells (spermatogonia/ spermatocytes/ spermatids/ spermatozoa) are absent. In general tubular architecture and supporting cells are not affected. Tubular fibrosis or hyalinization is also absent. Sertoli cells play important role in the development of a functional testis. The Sertoli cells secrete anti Mullerian hormone (AMH), inhibin B and lactate to ensure germ cell survival and function (60). In maturation arrest testes fail to produce mature spermatozoa due to interruption of germ cell development and differentiation. Here, germ cells are few or normal in numbers but development & differentiation into spermatozoa is interrupted. Testicular maturation arrest is classified into two distinct subtypes viz., early maturation arrest (mitotic/ meiotic arrest; development of germ cells do not advance beyond secondary spermatocyte) and late maturation arrest (post-meiotic/spermieogenesis arrest; differentiation of germ cells do not advance beyond round spermatid) (61). Defects in germ cell proliferation (mitosis) and function with subsequent impairment of meiosis or spermiogenesis cause testicular maturation arrest (51,61,62). Most

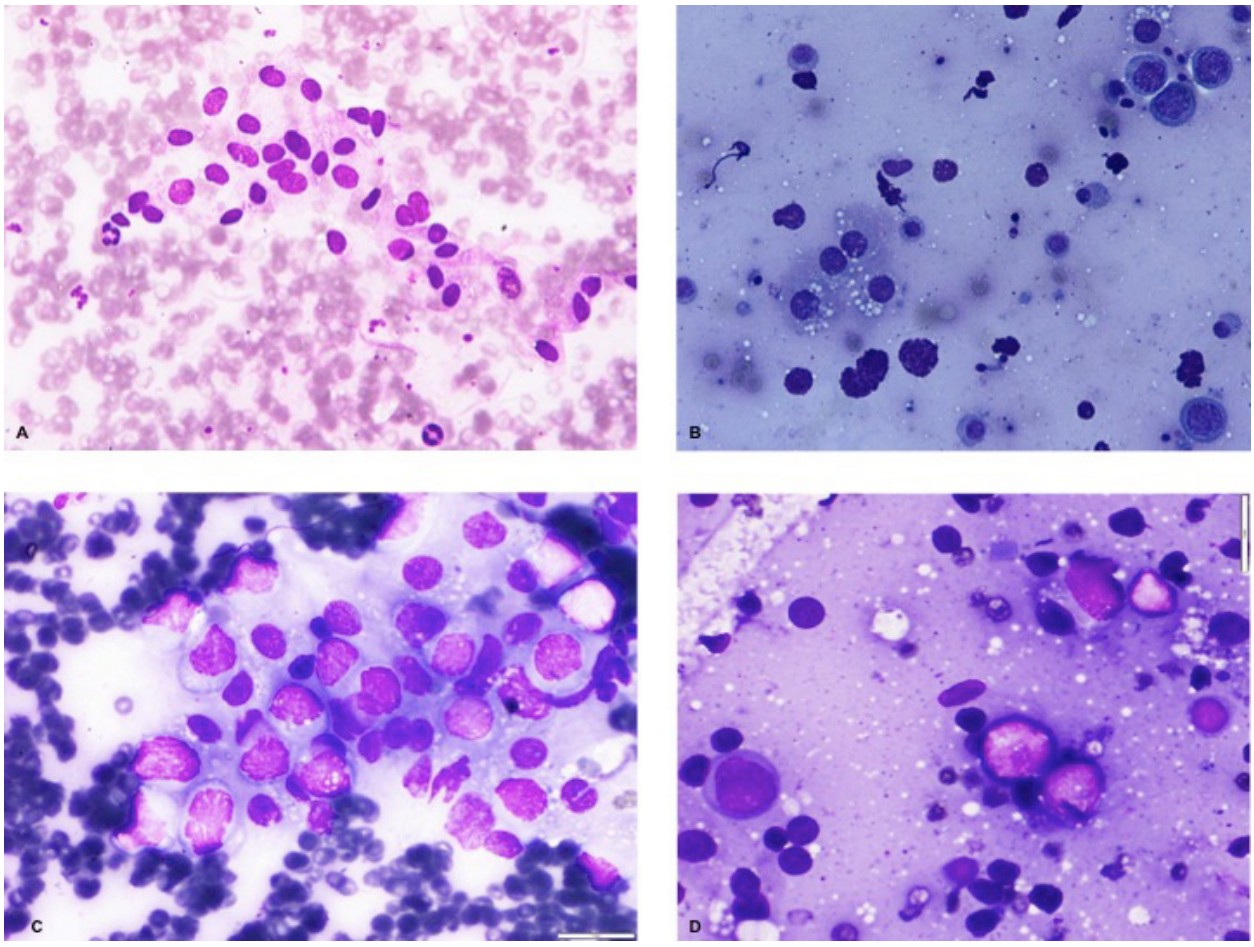

Figure 9. Fine Needle Aspiration Cytology microphotographs of primary testicular failure. A. Sertoli cell only syndrome (only Sertoli cells, no germ line cells). B. Hypospermatogenesis. (all type of cells but very few in numbers). C. Early maturation arrest (Sertoli cells and primary spermatocytes). D. Late maturation arrest (Sertoli cells and spermatids but no mature sperms). Courtesy of Prof. VK Iyer, Dept. of Pathology, AIIMS, New Delhi.

cases present as early maturation arrest at primary spermatocyte level but can occur earlier at spermatogonial (mitotic arrest) or later at spermatid level (spermiogenic arrest). Hypospermatogenesis is characterized by reduced number of germ cells (all types; spermatogonia, spermatocyte, spermatid and spermatozoa) but usually have normal Leydig cell number/ function. In testicular atrophy basement membrane of seminiferous tubules thicken. The germinal layer is mostly lost (few spermatogonia or primary spermatocytes may be found) and Leydig cells are few (63). However, often one may find differences in subtypes between testes viz., Sertoli cell only syndrome in one testis and tubular fibrosis in other testis or any combinations and these cases are usually labeled as mixed group. In addition many patients may present as complete germinal cell aplasia in some tubules whereas normal spermatogenesis in adjacent tubules (focal germinal cell aplasia) or some tubules with Sertoli cells only or hyaline sclerosis and other tubules with normal spermatogenesis or any other combination. This categorization should be considered as a description of histopathologic phenotypes of spermatogenetic failure and not as manifestations of disease entities. Sometimes, patients may present as hypospermatogenesis or maturation arrest initially and later as sertoli cell only syndrome or testicular fibrosis over a period of few years. Hence diagnosis may change with time. Sertoli cells play important role in development of functional testis. Sertoli cell only syndrome is a common finding of non-obstructive azoospermia. It is a histopathologic phenotype of spermatogenic failure described first by Del Castillo *et al.* (64). In complete germ cell aplasia, the tubules are reduced in diameter, contain only Sertoli cells and no germ cells are present. The primordial germ cells either do not migrate from the yolk sac into gonadal ridge or do not survive in the seminiferous tubules. Germ cell aplasia also can be focal with a variable percentage of tubules containing germ cells, but even in these tubules, spermatogenesis is often limited (65) and hence, such cases should be categorized as hypospermatogenesis.

Primary testicular failure can result from chromosomal abnormality (Klinefelter syndrome), Yq microdeletion, single gene mutation, etc. Klinefelter syndrome is the most common known cause of primary testicular failure (60,66). It affects approximately 1 in 1000 males (67) and is characterized by one extra X chromosome. Although an extra X chromosome (47,XXY) is the most common form, some men with Klinefelter syndrome have a greater number of X chromosomes or mosaicism (48, XXXY, 46,XY/47,XXY) (68). Infrequently, 46,XX males may present as Klinefelter syndrome (15). The phenotype varies with the number of extra X chromosomes and possibly also with the number of trinucleotide CAG repeats on the androgen receptor gene (a polymorphism). A longer CAG repeat sequence is associated with tall stature, low bone mineral density, gynecomastia and short penile length (69). Men with Klinefelter syndrome generally have small, firm testes resulting from damage to both seminiferous tubules and Leydig cells. Affected men have severely reduced sperm count and are under-virilized (70). Other chromosomal abnormalities associated with primary gonadal failure include the 45,X/46,XY karyotype (mosaicism), causing a syndrome characterized by short stature and other features of Turner syndrome (71). Because the testes may be streak, dysgenetic or normal, the phenotype varies from female to male.

Microdeletions of the long arm of the Y chromosome are now recognized as a relatively common cause of primary testicular failure (severe oligospermia and azoospermia), affecting up to 20% of men with infertility (72). Most microdeletions are mapped to the Yq11 region (named azoospermia factor or AZF). The Yq11 contains three sub-regions such as AZFa, AZFb and AZFc. Deletions of the AZFa or AZFb invariably produce azoospermia whereas deletions in the AZFc region cause infertility of varying severity, ranging from oligospermia to azoospermia. The AZFc deletion is the commonest microdeletion in humans (36). The AZFa region contains DDX3Y and USP9Y genes. These genes have important role in spermatogenesis and deletions of these genes are consistently observed with azoospermia (73,74). The Yq microdeletions have also been observed in men with cryptorchidism, varicocele and obstructions of the vas deferens (75). In our own study on 164 apparent idiopathic primary testicular failure cases we could find out underlying cause in about 21% cases (8.5% sex chromosomal abnormality, 11.6% Yq microdeletion i.e., AZFa,b,c and 0.6% combined sex chromosome abnormality as well as Yq microdeletion).

Normal male sexual differentiation and spermatogenesis require both normal androgen production and normal androgen receptors. The androgen receptor plays an important role in the differentiation of spermatids and their release from the seminiferous epithelium. The number of trinucleotide CAG repeats in exon 1 of the androgen receptor gene is inversely correlated with its transcriptional activity (69). A meta-analysis with 33 published studies revealed that men with spermatogenic disorders had longer CAG repeat lengths (55). Similarly, disorders of estrogen synthesis or action are also associated with spermatogenic defect. Impaired spermatogenesis has been observed in mice and men lacking a functional estrogen receptor alpha (76,77). In mice inactivating mutation in the aromatase enzyme also causes spermatogenic defect (78). Follicle stimulating hormone (FSH) receptor gene mutation too affects spermatogenesis (79). Men with myotonic dystrophy (an autosomal disorder associated with impaired motor function, cataract, premature balding, mild mental retardation and hypogonadism) also exhibit abnormal spermatogenesis (80). Mutations in the SYCP3 gene (involved in regulation of the synapse between homologous chromosomes during meiosis) have been implicated as a potential cause of spermatogenic defect (81). Other genes like DAZL (an autosomal homolog of the DAZ, deleted in azoospermia), PRM1 & PRM2 (protamines involved in chromatin compaction), TNP1 & TNP2 (transition nuclear proteins) and USP26 (deubiquitinating enzyme family) also are implicated with spermatogenic defects (81–83). We are working on various etiological aspects of primary testicular failure, including genotype phenotype co-relation using SNP microarray (84). We found detectable chromosomal cause in 8%, Yq microdeletion (mainly AZFb/c/bc) in 15%, Yq microduplication (mainly AZFc) in 9%, PAR 1 & 2 CNVs in 7% besides few CNVs containing spermatogenesis related genes like SPATA31A2-A5 (9p12). Testicular spermiation defect present as azoospermia despite normal spermatogenesis and in general they do not have any abnormality in chromosome or Yq microdeletion (85). Other well-known genetic mutations associated with male infertility are CATSPER1 (asthenozoospermia), SPATA16 & DPY19L2 (globozoospermia)/ AURKC (macro spermatozoa), etc.

3.2. Pre-testicular failure

The pretesticular (hypogonadotropic hypogonadism or secondary testicular failure) infertility originates from disorder in the pineal, hypothalamus, pituitary or adrenal glands. These extra-gonadal endocrine glands dysfunction have an adverse effect on spermatogenesis through aberrant hormonal action and responsible for infertility in less than 5% of cases. The genetic causes in this group are Kallmann Syndrome (KAL1: Xp22.3; KAL2/FGFR1: 8p11.2-p11.1; KAL3/PROKR2: 20p13; GnRH1: 8p21-p11.2; TAC3: 12q13–21; LEP: 7q31.2; NELF:

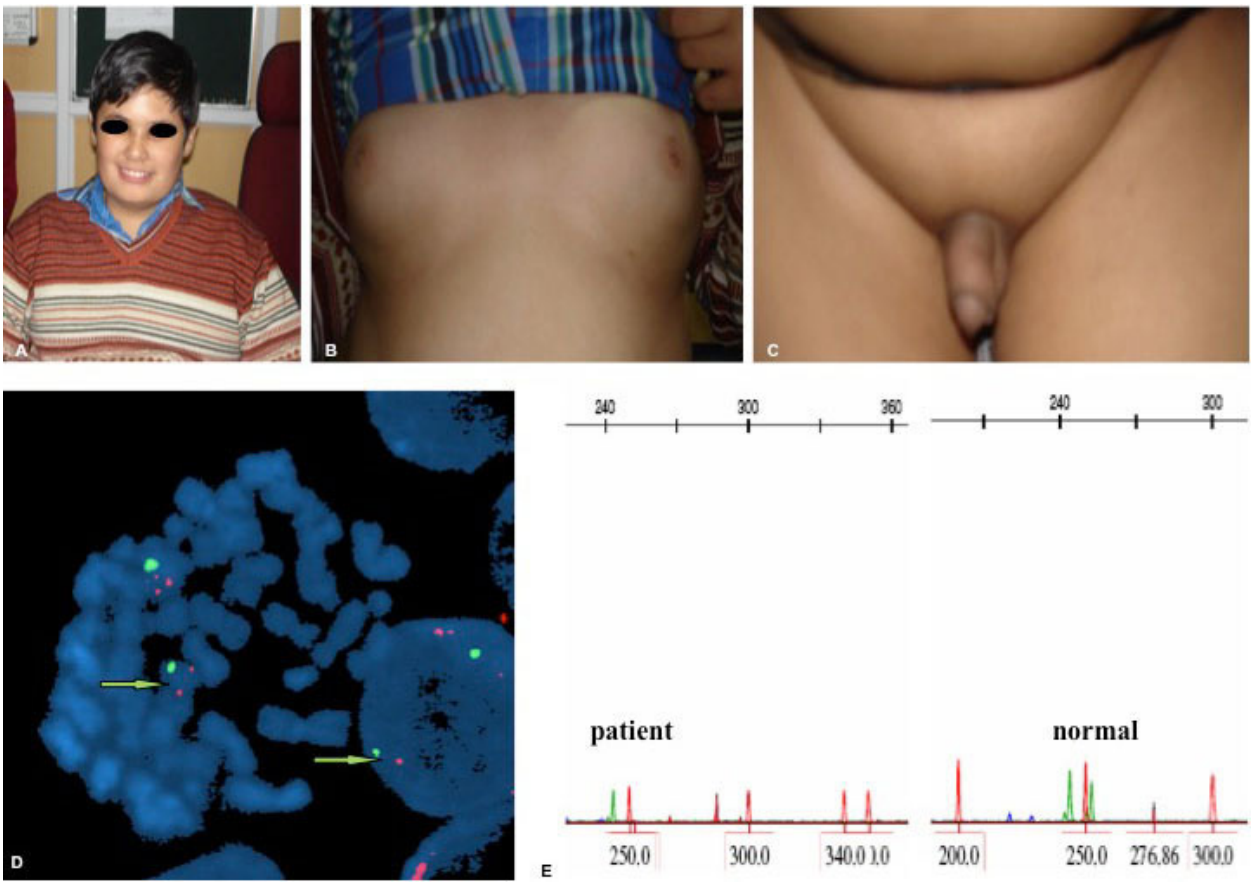

Figure 10. Prader Willi Syndrome (15q11–13 microdeletion; hypogonadotropic hypogonadism). A. Facial profile (delayed puberty). B. Gynecomastia. C. External genitalia (small penis and testes). D. FISH image showing hemizygous microdeletion of SNRPN probe (arrow on proximal red signal, close to centromere/green of chromosome 15; distal red split signal is from control/PML probe). E. Capillary electrophorogram using Prader Willi microsatellite marker (D15S11). Solitary 243bp peak (green color) in patient as against 243 & 252 dual peaks (green color) in normal sample.

9q34.3; CHD7: 8q12.1; DAX1: Xp21.3.-21.2; KiSS1: 1q32.1), CHARGE Syndrome (coloboma, heart defect, atresia of nasal choanae, retardation, genital anomaly & ear anomaly; CHD7 gene: chromo domain helicase DNA-binding protein; 67% of cases due to a CHD7 mutation), Prader Willi Syndrome (15q11–13) (Figure 10), Laurence Moon Syndrome (retinitis pigmentosa, spastic paraplegia, hypogonadism and mental retardation), Bardet–Biedl syndrome (14–15 different genes are involved), gonadotropin-releasing hormone (GnRH) insensitivity (GnRH Receptor mutation: delayed/ reduced/ absent puberty, low or complete lack of libido and infertility; predominant cause of idiopathic hypogonadotropic hypogonadism/IHH when does not present alongside anosmia; Table 3). Patients with hypogonadotropic hypogonadism show delayed puberty due to low sex steroid production along with low levels of serum gonadotropins. Patients with Kallmann syndrome also display an impaired sense of smell due to the developmental failure of the migration of GnRH neurons. Often patient may display cryptorchidism, sparse sexual hair, small testes, micropenis, hypogenitalism, hypogonadism and infertility. Kallmann syndrome is genetically heterogeneous, affects 1:8000 males and less common in females. Kallmann syndrome with ichthyosis in male is categorized as KAL1.

3.3. Post-testicular failure

The post-testicular causes (normo/eu-gonadotropic hypogonadism) of male infertility could be related to sperm motility, morphology, viability, acrosome, or other disorders or obstruction in genital tract. This group constitutes about 5–10% cases of male infertility. The genetic causes in this group are cystic fibrosis (CFTR gene mutations), globozoospermia **(**DPY19L2 gene homozygous deletion; 12q14.2 or SPATA16 gene deletion/mutation; 3q26.31), necrozoospermia (defect in apotosis or protamine condensation) or sperm chromatin or DNA damage (apoptosis, DNA repair, protamine, etc), etc (Table 4). CFTR mutation is common with non-obstructive azoospermia (10%) and characteristic of *congenital bilateral absence of vas deferens*/CBAVD (100% association).

Table 3. Pre-testicular genetic causes of male infertility

Parameters	Cytogenetic loci	Gene	Defect	Clinical Features	Reference
HH 1 (Hypogonadotropic hypogonadism 1)	Xp22.31	KAL1/ ANOS1/HH1	XL	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 2 (with or without anosmia)	8p11.23	FGFR1	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 3 (with or without anosmia)	20p12.3	PROKR2	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	310
HH 4 (with or without anosmia)	3p13	PROK2	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 5 (with or without anosmia)	8q12.2	CHD7	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 6 (with or without anosmia)	10q24.32	FGF8	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 7 (no anosmia)	4q13.2 or 8p11.23	GNRHR or FGFR1	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309,311
HH 8 (with or without anosmia)	19p13.3	KISS1R	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 9 (with or without anosmia)	9q34.3	NSMF	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in gonadotropin-releasing hormone	309
HH 10 (with or without anosmia)	12q13.3	TAC3	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 11 (with or without anosmia)	4q24	TACR3	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 12 (with or without anosmia)	8p21.2	GNRH1	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 13 (with or without anosmia)	1q32.1	KISS1	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 14 (with or without anosmia)	10q26.12	WDR11	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 15 (with or without anosmia)	2q14.3	HS6ST1	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 16 (with or without anosmia)	7q21.11	SEMA3A	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 17 (with or without anosmia)	5q31.3	SPRY4	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 18 (with or without anosmia)	3p14.3	IL17RD	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309
HH 19 (with or without anosmia)	12q21.33	DUSP6	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in gonadotropin-releasing hormone	309
HH 20 (with or without anosmia)	8p21.3	FGF17	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in GnRH	309

HH 21 (with or without anosmia)	20p12.1	FLRT3	AD	absent or incomplete sexual maturation; low levels of circulating gonadotropins and T; isolated defect in GnRH	309
HH 22 (with or without anosmia)	7q31.32	FEZF1	AR	absent or incomplete sexual maturation; low levels of circulating gonadotropins and testosterone; isolated defect in gonadotropin-releasing hormone	309
HH 23 with or without anosmia	19q13.33	LHB	AR	defects in gonadal growth and function, resulting in infertility decreased testis size, prominent Leydig cell hypoplasia, defects in expression of genes encoding steroid biosynthesis pathway enzymes, reduced T, and blockage of spermatogenesis at the round spermatid stage	312
HH 24 (with or without anosmia)	11p14.1	FSHB	AR	delayed puberty, underdeveloped muscles, no facial hair, small testicles, low serum T and FSH with high LH and azoospermia	313
Bardet-Biedl Syndrome 1	1p35.2	CCDC28B	DR/AR	modifier	314
Bardet-Biedl Syndrome 1	11q13.2	BBS1	DR/AR	retinal degeneration, male infertility and obesity	315
Bardet-Biedl Syndrome 2	16q13	BBS2	AR	obesity, retinitis pigmentosa, hypogonadism, polydactyly	316
Bardet-Biedl Syndrome 3	3q11.2	ARL6	DR/AR	modifier	317
Bardet-Biedl Syndrome 4	15q24.1	BBS4	AR	obesity, retinal degeneration and absent spermatozoa flagella	318
Bardet-Biedl Syndrome 5	2q31.1	BBS5	AR	obesity, retinitis pigmentosa, hypogonadism, polydactyly	319
Bardet-Biedl Syndrome 6	20p12.2	MKKS	AR	obesity, retinal dystrophy, polydactyly, learning difficulties, hypogenitalism and renal malformations	320
Bardet-Biedl Syndrome 7	4q27	BBS7	AR	obesity, retinitis pigmentosa, hypogenitalism	321
Bardet-Biedl Syndrome 8	14q31.3	BBS8/ TTC8	AR	retinitis pigmentosa, obesity, polydactyly, brachycephaly, hypogonadism	322
Bardet-Biedl Syndrome 9	7p14.3	PTHB1	AR	hypogenitalism, obesity, polydactyly, round face, retinitis pigmentosa	323
Bardet-Biedl Syndrome 10	12q21.2	BBS10	AR	hypogonadism	324
Bardet-Biedl Syndrome 11	9q33.1	TRIM32	AR	BBS phenotype	325
Bardet-Biedl Syndrome 12	4q27	BBS12	AR	early obesity, renal dysfunction, hypogonadism	324
Bardet-Biedl Syndrome 13	17q22	MKS1	AR	BBS phenotype	326
Bardet-Biedl Syndrome 14	12q21.32	CEP290	AR	BBS phenotype	327
Bardet-Biedl Syndrome 15	2p15	WDPCP	AR	BBS phenotype	328
Bardet-Biedl Syndrome 16	1q43-q44	SDCCAG8	AR	Hypogonadism, hypogenitalism	329
Bardet-Biedl Syndrome 17	3p21.31	LZTFL1	AR	hypogenitalism with micropenis and atrophic testes	330
Bardet-Biedl Syndrome 18	10q25.2	BBIP1	AR	BBS phenotype	331
Bardet-Biedl Syndrome 19	22q12.3	IFT27	AR	obesity, intellectual disability, polydactyly, retinitis pigmentosa, hypogonadism	332
Bardet-Biedl Syndrome 20	9p21	IFT74	AR	obesity, polydactyly, hypogonadism, intellectual disability, microcephaly and retinitis pigmentosa.	333
Adrenal Hypoplasia, Congenital, with HH	Xp21.2	DAX1	XLR	absence or interruption of normal pubertal development and abnormal spermatogenesis	334

MR, XL, syndromic 15	Xq24	CUL4B	XLR	small testes, with delayed sex development , muscle wasting	335
polyalanine deletions in SOX3combined pituitary hormone deficiency	Xq27.1	SOX3	Hemizygous deletion	X-linked mental retardation with growth hormone deficiency; normosmic Isolated hypogonadotropic hypogonadism	336
Scholte Syndrome	X	NK	XLR	mental retardation, short stature, an unusual skull shape, early anterior balding, unusual facial morphology, hypogonadotropic hypogonadism with small genitalia, and small patellae	337
Neuronal SCL-Like Protein 2	1p13.1	Nhlh2	AR	microphallic, hypogonadal and infertile	338
Obesity, morbid, due to leptin receptor deficiency	1p31.3	LEPR	AR	hyperphagia, severe obesity, alterations in immune function, and delayed puberty due to hypogonadotropic hypogonadism	339
Martsolf syndrome	1q41	RAB3GAP2	AR	cataract, MR, hypogonadism (micropenis, bilateral cryptorchidism, hypothalamic-pituitary insufficiency)	340
Senior-Loken syndrome 7	1q43-q44	SDCCAG8	AR	BBS phenotype	329
Leydig cell hypoplasia with pseudohermaphro.	2p16.3	LHCGR	AR	prevents normal sexual development Type II, micropenis to severe hypospadias	341
Follicle-Stimulating Hormone Receptor	2p16.3	FSHR	AR	variable degrees of spermatogenic failure, but, surprisingly, did not show azoospermia or absolute infertility	79
Culler-Jones syndrome	2q14.2	GLI2	AD	hypopituitarism and polydactyly cryptorchidism and microphallus	342,343
Woodhouse-Sakati syndrome	2q31.1	DCAF17	AR	hypogonadotropic hypogonadism,alopecia, diabetes mellitus, mental retardation	344
Microphthalmia, Syndromic 3	3q26.33	SOX2	AD	anophthalmia or microphthalmia with or without defects of the optic nerve, optic chiasm, and optic tract; hypoplasia of the anterior pituitary growth hormone &gonadotropin deficiency	345
Obesity with impaired prohormone processing	5q15	PCSK1	sporadic	watery diarrhoea, polyuria and polydipsia, obesity, low serum cortisol level and ACTH precursor levels, hypothalamic hypothyroidism, HH, *etc*	339
Pituitary hormone deficiency, combined, 2	5q35.3	PROP1	AR	sequential loss of anterior pituitary tropic hormones (GH/GnT; TSH & later ACTH)	346
Cerebellar ataxia & HH	7p22.1	RNF216	AR	dementia, and variable ataxia, chorea and hypogonadotropic hypogonadism	347
William syndrome region	7q11.23	FKBP6	AR	chromosome pairing in meiosis	348
Alopecia, neurologic defects, and endocrinopathy syndrome	7q32.1	RBM28	AR	alopecia, neurologic defects, and endocrinopathy central hypogonadotropic hypogonadism with delayed or absent puberty and central adrenal insufficiency	349
Obesity, morbid, due to leptin deficiency	7q32.1	LEP	AR	obese, hyperphagia , hypogonadotropic hypogonadism with sterility, infertility due to hypothalamic-pituitary hormone insufficiency; no beard, scanty pubic and axillary hair, bilateral gynecomastia and small penis & testes	350,351
CHARGE syndrome	7q21.11, 8q12.2	SEMA3E CHD7	AD	HH, manifested by hypogenitalism and gonadotropins	352
Histiocytosis-lymphadenopathy plus syndrome	10q22.1	SLC29A3	AR	histiocytosis, lymphadenopathy, hypertrichosis, diabetes, hypogonadism,	353
Leukodystrophy, hypomyelinating, 7, with oligodontia and / or HH	10q22.3	POLR3A	AR	spasticity, ataxia, tremor, and cerebellar signs, hypodontia or oligodontia and HH	354
IMAGE syndrome	11p15.4	CDKN1C	AD	dysmorphic features, bilateral cryptorchidism, a small penis and HH	355

Ciliary dyskinesia, primary, 34	11q13.4	DNAJB13	AR	infertility	356
Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or HH	12q23.3	POLR3B	AR	cerebellar ataxia and mild intellectual disabilities associated with diffuse hypomyelination, oligodontia and/or HH	357
Small Nucleolar RNA, C/D Box, 116-1 (PWCR1)	15q11.2	SNORD116-1	deletion	partial hypogonadotropic hypogonadism, and growth failure	358
Prader-Willi syndrome	15q11.2	NDN, SNRPN, *etc*	deletion of the paternal copies	diminished fetal activity, obesity, muscular hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, and small hands and feet	359
Aromatase excess syndrome	15q21.2	CYP19A1	AD	gynecomastia, a premature growth spurt, early fusion of epiphyses, and decreased adult height; HH	360
Polyendocrine-polyneuropathy syndrome	15q21.2	DMXL2	AR	HH with central hypothyroidism, severe hypoglycemia progressing to nonautoimmune IDDM, peripheral demyelinating polyneuropathy and mental retardation	361
Cingulin-Like 1	15q21.3	CGNL1	AD	gynecomastia of prepubertal onset, hypo-gonadotropic hypogonadism, estrogen excess	360
Spinocerebellar ataxia, autosomal recessive 16	16p13.3	STUB1	AR	spinocerebellar ataxia between 14 and 19 years of age and hypogonadism	362
Mulibrey nanism	17q22	TRIM37	AR	growth reduction, mental retardation, moderate adiposity, acanthosis nigricans, HH	363
Boucher-Neuhauser / Laurence-Moon/ Oliver-McFarlane syndrome	19p13.2	PNPLA6	AR	spinocerebellar ataxia, hypogonadotropic hypogonadism and visual impairment	364
Oliver-McFarlane syndrome	19p13.2	PNPLA6	AR	trichomegaly, severe chorioretinal atrophy and multiple pituitary hormone deficiencies, including growth hormone, gonadotropins, TSH	365
Johnson Neuroectodermal Syndrome	NK	NK	AD	anosmia and HH, conductive deafness, alopecia, protruding ears, microtia, and/or atresia of the external auditory canal	366
Arhinia, Choanal Atresia, and Microphthalmia	NK	NK	sporadic	severe hypoplasia of the nose and eyes, palatal abnormalities, deficient taste and smell, inguinal hernias, HH with cryptorchidism, and normal intelligence	367

Table 4. Post-testicular genetic causes of male infertility

Parameters	Cytogenetic loci	Gene	Defect	Clinical Features	Reference
A-kinase anchoring protein 4	Xp11.22	AKAP4	XL	sperm motility, asthenospermia	368
G protein-coupled receptor 64	Xp22.13	Gpr64	XL	reduced fertility, complete infertility over time, defect in luminal fluid reabsorption, resulting in a build-up of fluid within the testis and accumulation of spermatozoa within the efferent ducts	369
Adhesion G Protein-Coupled Receptor G2	Xp22.13	ADGRG2	XL	reduced fertility; accumulation of spermatozoa within the efferent ducts	369
hook microtubule tethering protein 1	1p32.1	HOOK1	AR	abnormal spermatozoon head shape	370
Apolipoprotein E receptor-2	1p32.3	apoer2		flagellar angulation and impaired motility	371
TEKTIN 2	1p34.3	TEKT2	AR	abnormal sperm morphology and function, with frequent bending of the sperm flagella & marked defects in motility	221
Mitochondrial Capsule Selenoprotein	1q21.3	SMCP	AR	infertility due to reduced motility of spermatozoa & decreased capability of spermatozoa to penetrate oocytes	372
AGFG1	2q36.3	HRB	AR	infertile and displayed round-headed spermatozoa that lacked an acrosome	373

Dynein, Axonemal, Heavy Chain 1	3p21.1	DNAH1	AR	reduced straight line velocity and progressive movement, infertile	374
NOP2/Sun RNA methyltransferase family member 7	4p14	Nsun7		defectsin motility	375
Adenosine Deaminase Domain-Containing Protein 1, testis specific	4q27	ADAD1	AR	defects in motility and could bind but not penetrate the zona pellucida	238
Calmegin	4q31.1	Clgn	AR	spermatogenesis and infertility	376
cysteine rich secretory protein 2	6p12.3	CRISP2		asthenospermia	377
c-ros tyrosine kinase receptor	6q22.1	Ros1		infertile, sperm exhibit flagellar angulation	378
Estrogen receptor-α	6q25.1-25.2	Esr1		dilution of sperm	379
Parkin coregulated gene	6q26	PACRG	Del/AR	spermatozoan flagella, asthenospermia	380
Cystic fibrosis/ CBAVD / Young syndrome	7q31.2	CFTR	AR	meconium ileus, biliary cirrhosis, emphysema, high sweat electrolyte & infertility; congenital bilateral absence of the vas deferens	381
ADAM metallo-peptidase domain 2	8p11.22	ADAM2 & 3	AR	sperm–egg fusion defect	382
Ciliary dyskinesia, primary, 19	8q24.22	LRRC6	AR	variable infertility and immotile cilia asthenospermia	383
casein kinase 2 alpha 2	16q21	Csnk2a2	AR	globozoospermia; sperm head morphogenesis abnormality	384
Septin 4	17q22	Sept4	AR	sterile, and their sperm showed defective morphology and motility	385
glyceraldehyde-3-phosphate dehydro-genase,spermatogenic	19q13.12	GAPDS		required for sperm motility and male fertility	386
acrosin	22q13.33	ACR	AR	sperm are not capable of binding and penetrating the zona pellucida	387
Young Syndrome	NK	NK	AR	infertile, normal spermatogenesis (not associated with CFTR mutations)	388
CD59b antigen	NK	Cd59b	AR	teratozoospermia, asthenozoospermia; abnormal sperm morphologies	389
Nuclear oxysterol receptor LXR α and β	NK	lxr		cauda spermatozoa; exhibited detached heads, flagellar angulation	390

4. COPY NUMBER VARIATIONS (CNVs) WITH MALE INFERTILITY

CNVs are submicroscopic chromosome loss or gain that involves several genes. The causal relation between submicroscopic chromosomal rearrangements and impaired sperm production are due to alteration in gene function. CNVs produce effect through loss of gene function or de-masking a recessive mutation on the homologous chromosome or gene disruption or position effect (86). We are working in male infertility using SNP microarray on DNA samples obtained from peripheral blood nucleated cells. The study finds an association between CNVs of PAR 1, 2 & 3 with testicular maturation arrest (84). In another study using X chromosome specific high-resolution *comparative genomic hybridization* (CGH) array, authors found significantly more X chromosome CNVs in infertile men than controls (87). We have also observed preponderance of CNVs in sex chromosomes, in particular Y chromosome. This indicates that sex chromosomes are extremely important in investigation of azoospermia. Sex chromosome CNVs may cause defective recombination or meiosis and thereby spermatogenic failure (87–90). We have also observed sex chromosome abnormalities, AZF deletions (mostly AZFc), CNVs in pseudo-autosomal regions (PAR 1, 2 and 3), AZFc gain and CNVs containing specific testes/spermatogenesis loci containing genes like SPATA31A2-A5. In male meiosis, the X and Y sex chromosomes do pair in prophase I, thus ensuring that at anaphase I each daughter cell receives one sex chromosome, either the X or the Y (91). The XY pairing is mostly end-to-end and is made possible by a region of homology between the X and Y chromosomes at the tips of their short arms (Xp22.3 and Yp11.32)

called PAR 1 (92) and long arms (Xq28 and Yq12) called PAR 2 (93). In some individuals another area in sex chromosomes pairs during meiosis known as PAR 3 (Yp11.2/Xq21.3). Aberrations in chromosome structure or number that disrupt meiotic synapsis are usually associated with gametogenic failure (94) and the impairment of sex chromosome pairing (synapsis) during meiosis is one of the etiological factors underlying maturation arrest (95). Aberrations in sex chromosome number or structure disrupt sex chromosome pairing (synapsis) during meiosis resulting in gametogenic failure (94,95). Errors in meiotic synapsis and recombination are recognized by checkpoints and induce cell cycle arrest and/or apoptosis (96). The sex chromosome pairing in the PAR appears to be critical for meiosis and therefore for spermatogenesis as well. CNVs of the PAR region probably lead to disruption of synapsis by structural aberrations resulting in failure of XY pairing, meiotic arrest and male sterility. PAR regions are rich in genes and escape X inactivation to maintain dosage compensation (97,98). PAR genes (PAR 1: AKAP17A, ASMT, ASMTL, CD99, CRLF2, CSF2RA, DHRSX, GTPBP6, IL3RA, P2RY8, PLCXD1, PPP2R3B, SHOX, SLC25A6, XG, ZBED1; PAR 2: IL9R, SPRY3, VAMP7, AVPR2, CXYorf1 and PAR 3: PCDH11Y, TGIF2LY) are dosage sensitive and hence CNVs (deletions or duplications) of PARs result in under or over expression of genes and could lead to pathological phenotype. PAR1 harbors PPP2R3B (PR48) gene, which has a potential role in spermatogenesis. Functional evidence supports its involvement both in mitosis and meiosis (cell cycle negative regulator). PPP2R3B (PR48) encodes for a subunit of the protein phosphatase 2 (PP2) protein complexes (99). PPP2R3B maintains pool of dephosphorylated CDC6 replication licensing factor (99). CDC6 phosphorylation and dephosphorylation is necessary for the mitotic G1 to S phase transition (100) and the overexpression of PPP2R3B disturbs cell cycle progression, causing a mitotic arrest at G1 phase. Expression analysis of testis biopsies supports involvement of PPP2R3B in mitosis (101). PAR 2 contains various functional genes like H2AFB1 (2-copies), H2AFB2 (2), H2AFB3 (2), F8A1 (2), F8A2 (2), F8A3 (2), TMLHE (2), SPRY3 (1), IL9R (2) and VAMP7. The genes in PAR 2 seem not to be directly linked to cell cycle, meiosis and/or spermatogenesis, except H2AFB family genes (histone family, member B1, B2 and B3). Unlike canonical histones that function primarily in genome packaging and gene regulation, H2AFB, a variant histone has role in DNA repair, meiotic recombination, chromosome segregation, transcription, sex chromosome condensation and sperm chromatin packaging (102). The imbalances of these genes caused by PAR 2 CNVs may have an impact on spermatogenesis leading to spermatogenic arrest. Impairment of spermatogenesis also can be explained through a structural defect affecting recombination event in gene independent manner. Hence, it is important to study CNVs of pseudo-autosomal regions besides sex chromosome aneuploidy and mosaicism.

The role of gain in AZFc region as underlying etiopathology in nonobstructive azoospermia is controversial. Lin *et al.* (103) reported that men with partial AZFc duplications that result in increased AZFc gene copies were at increased risk for spermatogenic impairment. Similarly, men with only AZFc duplications and without any AZFc deletion, resulting excess copies/ over dosage of DAZ genes, are in a disadvantageous position for normal spermatogenesis (104). Other CNVs containing genes like MYRIP, LRRC4C, RNA LOC100507205, EDDM3A, EDDM3B, HLA-DRB1, HLA-DQA1, POTE B, GOLGA8C, DNMT3L, ALF, NPHP1, NRG1, RID2, ADAMTS20, TWF1, COX10, MAK, DNEL1, SUN5 (20q11.21), SPATA6 (1p33), SPATA4 (15q26.2), SPATA12 (3p14.3), SPATA17 (1q41), SPATA8 (15q26.2), SPATA, TEX101 (19q13.31), BEX2/1 (Xq22.1), MAATS1 (3q13.33), RNF141 (11p15.4), PBK (8p21.2), C17orf75 (17q11.2), SPATA42 (1p13.3), UBE2B (5q31.1), KIT (4q12), SPATA31A, etc are reported with spermatogenic arrest (105–108). Many more reports observed an increased frequency of CNVs in infertile men compared to controls (88,109,110) including sex chromosomes & deletion of Xp11.23 (89) (Table 5).

5. EPIGENETIC MODIFICATION IN MALE GAMETOGENESIS AND MALE INFERTILITY

Epigenetic is alteration in the gene function without affecting basic DNA sequence i.e., change in phenotype without changing genotype. These alterations are mainly addition of different molecules to the DNA, which then changes the regulation of gene function. The main epigenetic mechanisms of gene regulation are DNA methylation, histone modifications and non-coding RNAs. In DNA methylation DNA methyl transferase enzyme adds methyl group from s-adenosyl methionine as methyl donor to 5' carbon of cytosine resulting in CpG dinucleotide. DNA methylation is involved in genomic imprinting, X chromosome inactivation and gene silencing. Histone modification requires various enzymes like histone methyltransferase, histone acetyl transferase, ubiquitin enzymes, etc and is involved in DNA methylation, acetylation, phosphorylation, ubiquitinylation, etc and regulate DNA replication, repair, recombination and gene expression. Non-coding RNA do not code for protein but regulate gene expression and plays role in imprinting, X inactivation, gene silencing, etc.

Most important contribution of sperm to the zygote, beside nucleus, is functional centrosome. Functional centrosome is important for orderly chromosome segregation. Immature sperm does not have a functional centrosome, thus if used for

Table 5. Genomic (copy number variations) causes of male infertility

Cytogenetic loci	Genes	CNV/SNP	Clinical Features	Reference
Xp11.4, Xp11.22, Xq22.1, Xq22.2, Xq22.3, Xq23, Xp22.33 (del), Xp21.3 (del/dup), Xp11.3, Xq11.1, Xq12, Xq22.3–q23, (del), Xq24, Xq25 (del/dup), Xq26.2 (del), Xq26.3, Xq27.1, Xq28 (del), Yp11.2, Yp11.223, Yp11.23	TSPAN7, SSX7, SPANXN5, BEX1, NXF3, H2BFWT, PAK3, TRPC5, SSX2, XAGE5, XAGE3, FAM156A, FAM156B, BEX4,TCEAL8, TCEAL5, BEX2, TCEAL7, TMSB15B, H2BFXP, H2BFM, NRK, SERPINA7, MUM1L1, ODZ1, MIR320D2, XG, GYG2, SYAP1, EFHC2, MSN, HEPH, CAPN6, DCX, ALG13, STAG2, MBNL3, RBMY2EP (AZFb/bc)	private sex chromosomal (duplication/ deletion)	SCOS & severe oligospermia	88
3p11.1, 6p21.31, 12q23.1, 8q24.3, 16q22.1	EPHA3, ANKS1A, ANKS1B, PLEC, PRMT7	recurrent autosomal	SCOS & severe oligospermia	88
1p36.32, 1p13.3, 6p21.32, 12p12.1, 20p13,	PEX10, PRMT6, SOX5,	strongly signify-cant SNPs	non obstructive azoospermia	305,306
1p34.3, 1p13.2, 2p22.2, 3q24, 12q24.31, 17p11.2	THRAP3/C1orf113, SYT6, FAM82A1, PLSCR2, SIRT4, C17orf51	CNVs (deletion/ duplication)	maturation arrest	110
Yq11, Yp11.2	AZF, gr/gr and TSPY1 CNV	CNV	spermatogenic failure	307
Xp22.33, Xq28	VAMP7	PAR1 & PAR2 deletion	azoospermia & oligozoospermia	87
9p24.3	DMRT1, SPACA5	deletion/ duplication	spermatogenic impairment	89
1p31-p22	CLCA4 (modifier of CFTR gene expression)	deletion	azoospermia/ cryptorchidism	308
Yp11.32/ Xp22.3 (PAR1); Yq12/ Xq28 (PAR2); Yp11.2/ Xq21.3 (PAR3)	AKAP17A, ASMT, ASMTL, CD99, CRLF2, CSF2RA, DHRSX, GTPBP6, IL3RA, P2RY8, PLCXD1, PPP2R3B, SHOX, SLC25A6, XG, ZBED1; IL9R, SPRY3, VAMP7, AVPR2, CXYorf1; PCDH11X, PCDH11Y, TGIF2LX, TGIF2LY	CNV (deletion or gain)	azoospermia/ maturation arrest	84
Xq27.1-q27.2	SPANXC	deletion	azoospermia/ maturation arrest	84
15q15.3	CATSPER2	deletion	azoospermia/ maturation arrest	84
9p12	SPATA31A2-A5	deletion	azoospermia/ maturation arrest	84
Yq11.23 (AZFc)	CDY1B; CYorf17; EIFIAY; PRY, PRY2; RBMY1A1, B, D, E,F,J; RPS4Y2; BPY2,2B; DAZ1,2,3; KDM5D; TTTY3, 4,6,17; TSPY1; CSPG4LY; GOLGA2LY	CNV (deletion or gain)	azoospermia/ maturation arrest	84

fertilization during assisted reproduction, will lead to error in chromosome segregation and aneuploid embryo (111). Abnormal centrosomes may also cause cleavage arrest (112). The imprinted regions of DNA are reset in every reproductive cycle (113). Chromatin packaging is another essential step in sperm development and during the process histones are replaced by protamines. Abnormalities in protamines (protamine 1/P1 and protamine 2/P2) affect spermatogenesis (114). P2 is associated with sperm DNA damage and abnormal packaging of chromatin (115). P1 or P2 gene mutation or alteration in P1 & P2 protein ratio may also cause male infertility (116).

There are four windows of susceptibility of epigenetic effect (117) in male reproduction. The first window is during development of gonad, when primordial germ cells undergo genome wide epigenetic erasure during migration to the genital ridge. The second window is during prepuberty. The third window is during spermatogenesis, specifically during transition from spermatogonium to spermatocytes & spermiogenesis stage. Finally, the fourth window is represented by the peri-fertilization period.

Alterations in sperm count, morphology, DNA fragmentation and aneuploidy could also be related to epigenetic mechanisms occurring at different stages of spermatogenesis. The last phase of spermatogenesis is spermiogenesis, which is characterized by a morphological transformation of the round spermatid. This leads to the production of mature sperm, characterized by the tail/ flagellum and the acrosome, prerequisites for sperm motility and fertilization. During spermiogenesis sperm DNA also undergoes condensation due to the replacement of over 90% of the histones with protamines (118). This modification improves sperm motility, protects from oxidative stress as well as toxic agents and blocks transcriptional activity of the sperm DNA (119).

The effect of epigenetic modification of sperm can affect reproduction and also transmits to offspring. Several environmental and lifestyle factors such as stress, physical activity, alcohol intake, smoke, shift work, etc may affect male fertility (120) and in many cases the effect is mediated through epigenetic modifications (121).

Epigenetic alterations could account for at least a portion of cases of male infertility in which no genetic abnormalities are detected. Alterations of genomic imprinting cause several diseases mainly involving fetal growth (growth abnormalities: underweight or overweight), hormonal balance (e.g., Albright hereditary osteodystrophy, pseudohypoparathyroidism 1A, transient neonatal diabetes mellitus) or behavior (e.g., Prader Willi syndrome, Angelman syndrome) (122). An increased incidence of Angelman syndrome or Beckwith Wiedemann syndrome is reported in offspring from ICSI/ART procedures (123,124). Epigenetic reprogramming through mitotic or meiotic crossover during spermatogenesis has important effect on the normal fertilization as well as embryonic development and its dysregulation leads to infertility, abortion, malformation, growth disturbance (over or underweight), premature aging, cancer, etc. ART procedures, in particular intracytoplasmic sperm injection, cloning (with somatic nucleus), induced pluripotent stem cell derived offspring, etc produce epigenetic abnormalities. Environmental agents can also influence human heredity (125), mainly through epigenetic mechanism.

6. EVALUATION

The evaluation of a male with infertility is performed to determine the etiology, prognosis, treatment options and counseling. The first step of evaluation is semen analysis. Azoospermia is diagnosed when no spermatozoa can be detected on high power microscopic examination of centrifuged (for 15 minutes at a centrifugation speed of 3000g or greater) seminal deposits on at least two occasions at an interval of 3 months (preferably). The initial important evaluation to determine cause & type should include fertility history, mumps, cryptorchidism, genital trauma or history of inguinal/scrotal surgery, genital infection such as filariasis/tuberculosis, gonadotoxin exposure such as radiation/chemotherapy or heat exposure and current medications. Family history of cystic fibrosis is also considered. Physical examination should include secondary sex character, body mass index, testis (size & consistency), epididymis (nodule/cyst/varicocele), vasa deferentia (present/absent), etc. The initial hormonal evaluation should include measurement of serum testosterone, prolactin and FSH levels followed by inhibin B &/or AMH estimation. One ultrasound-doppler study should be advised to exclude varicocele. Finally testicular fine needle aspiration cytology (FNAC) or testis biopsy is required to confirm diagnosis and categorize. Figure 11 reproduces algorithms that may assist in the assessment and direct type of investigations for infertile male. Table 6 outlines important genetic tests that are worth investigating in order to find out underlying etiology of male infertility that may assist in counseling the patient and probably management of infertile male as well.

FSH is the classical endocrine parameter to discriminate testicular impairment of spermatogenesis from obstructive as well as pretesticular disorders. FSH level is also a valuable predictive marker of the histological picture of the testis (126) but due to wide overlap between values in normal control and reduced spermatogenesis limits its diagnostic accuracy (127). Inhibin B is another important spermatogenesis marker in men. Inhibin B is secreted from the Sertoli cells of the testes. Inhibin B selectively suppresses the secretion of FSH, has local paracrine actions on the gonads and appears to be involved in the regulation of gametogenesis. In adult male, serum level of inhibin B is stable throughout life. Inhibin B expression and secretion in men is positively correlated with Sertoli cell function & number, sperm number and spermatogenic status and negatively correlated with FSH. It is a good marker of spermatogenesis and may offer an improved diagnosis of testicular dysfunction (126,128). Anti Mullerian Hormone (AMH) is produced from the Sertoli cells of testes in male. AMH blood concentration decreases dramatically during puberty and persists at low value in adult. Undetectable or very low AMH reflects a primary alteration in Sertoli cell function. However, its value in men with maturation arrest or hypospermatogenesis or oligozoospermia is controversial (129).

In our experience inhibin B seems to be a good predictor/marker of primary testicular failure. In *Sertoli cell only syndrome* (SCOS) FSH is also a good marker along with inhibin B (126). The classic predictors of spermatogenesis are testicular size, semen analysis, FSH level and testicular histology. However, in our experience we have found frequently contradicting findings viz., small testicular size with better seminal parameters or SCOS with occasional sperm in semen. We have observed lower predictive value of FSH with maturation arrest (MA) as well as hypospermatogenesis (HS). The FSH value is often normal in these subgroups. Inhibin B seems a better predictor in these situations. This is also supported by observation of more accurate prediction of the presence of testicular spermatozoa in nonobstructive azoospermia with the level of serum inhibin B. Estrogen is involved in the negative feedback effects of testosterone and controls pituitary gonadotropin secretion. The role of estrogen in male is still a matter of debate even though there is a growing body of evidence suggesting that estrogen plays a role via

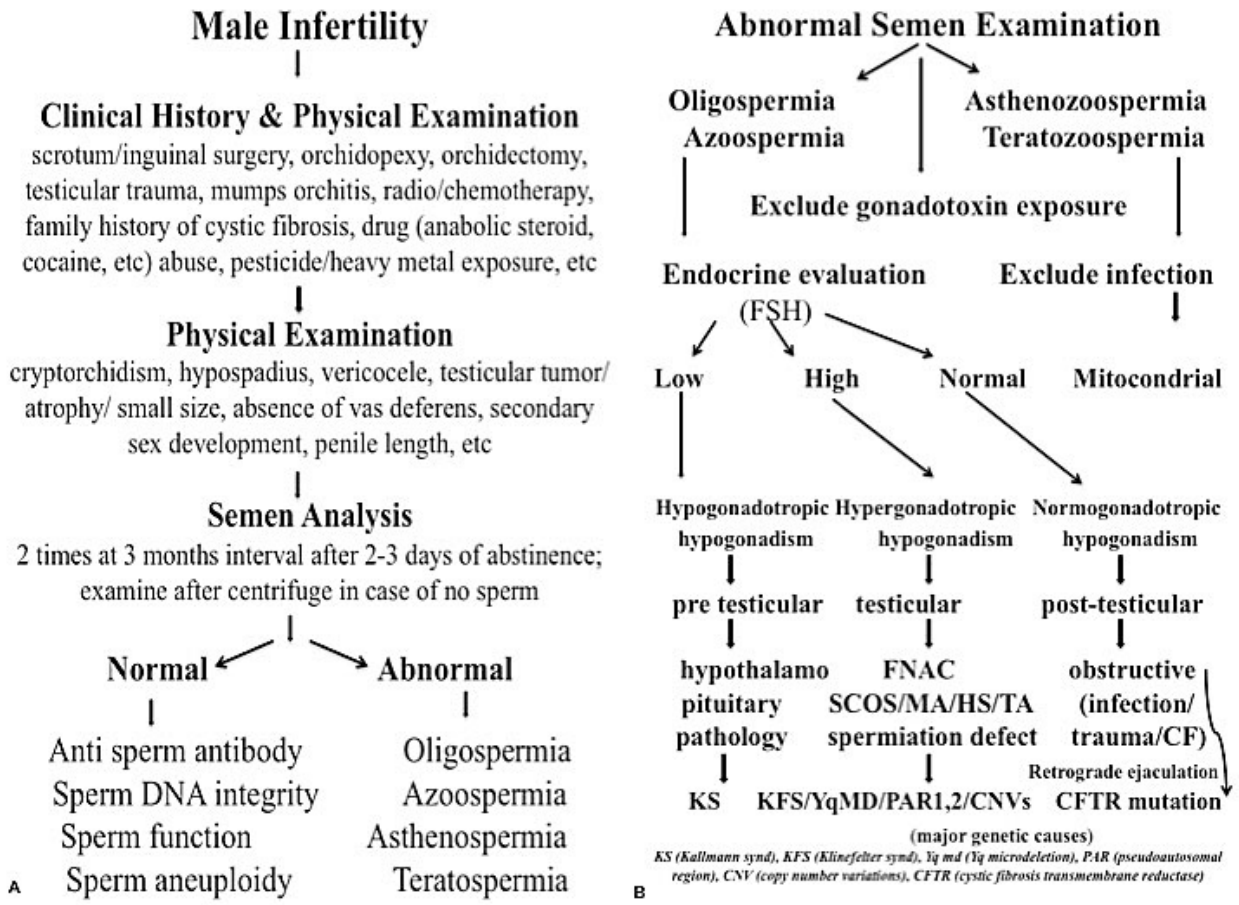

Figure 11. Algorithm for the workup of the infertile male. A. Algorithm may be considered on initial assessment. B. Algorithm may be considered in patient presented with abnormal semen examination.

their specific receptor (ERα and ERβ) that are present throughout the genital tract besides its effect on gonadotropin secretion. In our experience estrogen plays a role in some early maturation arrest cases as evidenced by elevated level of estradiol.

Various tests are now available to explore the genetic cause of male infertility. Genetic tools used for the evaluation of male infertility are chromosomal analysis (conventional cytogenetics & FISH), Yq microdeletion, CGH/SNP microarray (DNA microarray), epigenetic/methylation microarray (DNA methylation microarray), long noncoding RNA (lncRNAs) microarray, mutation analysis by PCR/ DNA sequencing and next generation sequencing (NGS) for gene panels/whole exome or whole genome sequencing. Conventional cytogenetics is usually carried out using lymphocyte cell culture for 72 hours. A mitotic inhibitor (colchicine) is added after 70 hours of culture, cells are incubated again for 2 hours to arrest cells in metaphase Thereafter the cells are treated with hypotonic solution (50 mMol KCL) followed by fixation in Carnoy's solution (methanol: acetic acid). Fixed cells are spread over glass slide, banded with Geimsa Tripsin Geimsa (GTG) staining and are evaluated under light microscope for abnormalities. FISH is carried out most frequently using commercially available FISH probes on metaphase spread chromosomes or interphase cell nuclei. The probe and nuclear DNA are denatured together on to a glass slide, hybridized overnight at 37°C, washed with NP40, dehydrated in ethanol series, mounted in antifade containing DAPI (4,6 diaminidino-2- phenylindol) and are screened under fluorescent microscope using plan-apochromatic objective and single band pass filter for DAPI, FITC, TRITC, etc flurochromes (depending upon flurochrome used for labeling FISH probes). Presence of two signals in 100 per cent metaphases and/ or 90 per cent interphase cells are considered as normal. Sequence tagged sites (STS) PCR is performed to confirm AZF deletion using commercially available 20 primer pairs for known STS (Promega, USA) or 6 primer pairs (2 each for AZFa, AZFb & AZFc regions). Absence of amplification proves deletion. PCR technique is used to amplify a single copy or a few copies of a piece of DNA (usually few hundred base pair size) to several orders of magnitude for easy visualization. It is based on the ability of DNA polymerase enzyme

Table 6. Type of pathology and important genes/genomic alterations associated with male infertility

Pre-testicular failure (hypogonadotropic hypogonadism) Hypothalamo-pituitary defect
• Kallmann syndrome with or without anosmia: KAL1, FGFR1, PROKR2, CHD7, FGF8, GNRH1, GNRHR, KISS1, KISS1R, NSMF, TAC3, TACR3, WDR11, HS6ST1, FGF17, FLRT3, LHB, *etc* • Bardet-Biedl Syndrome: CCDC28B, BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS10, BBS12, ARL6, MKKS, TRIM32, MKS1, BBIP1, IFT27, *etc* • PWS: SNORD116-1, NDN, SNRPN, *etc* • Others: PCSK1, PROP1, FKBP6, DAX1, SOX2, SOX3, LEPR, FSHR, GLI2, RBM28, SLC29A3, POLR3A, POLR3B, CYP19A1, PNPLA6, *etc*
Primary testicular failure (hypergonadotropic hypogonadism) Testicular defect
• Maturation arrest (early): SYCE1, TEX11, Sycp1, Sycp3, MSH4, MSH5, BOLL, MLH1, MLH3, DAZL, MORC1, CLCN2, PRDM9, STAG3, Cks2, H2AFX, Ccna1, Cpeb, SNRPA1, BSG, CADM4, Bax, Spo11, DMC1, MEI1, MOV10L1, *etc* • Maturation arrest (late): ZMYND15, CDY1, CDY1B, CDY2A, CDY2B, HSFY1, ADAD1, CAMK4, TBPL1, PAPOLB, CREM, DDX25, PIWIL1, RNF17, BCL2L, STYX, HSPA2, Cyp19A1, PRM1, TBC1D20, *etc* • Sertoli cell only syndrome (SCOS): USP26, USP9Y, DBY, UTY, DAZ4, NANOS2, NANOS3, *etc* • Hypospermatogenesis (HS): EGF, BUB1B, *etc* • Testicular atrophy: SOX3-RELATED, Bmp8b, LMNA, DDX4/VASA, SCA32, DMRT1, *etc* • Gonadal dysgenesis: Dhh • Non obstructive azoospermia/oligozoospermia (undefined): SYCP3, NR5A1, TAF4B, BPY2, TSPY, DAZ1/2/3, RBMY1A1, NR0B1/DAX1, AR, GNPAT, NPAS2, RAD6B/UBE2B, Fkbp6, Slc4a2, PIWIL2, CKMT1A, INSL3, DMPK, *etc* • Other genetic study: Commonest cause: Yq microdeletion- AZFa (SCOS), AZFb (MA), AZFc (MA, HS, oligospermia) • Second commonest cause: Chromosomal abnormality- sex chromosome abnormality, translocations, *etc* • Other common cause: copy number variation in pseudoautosomal regions
Spermiation defect
• Dnaja1, KATNB1, *etc*
Post-testicular failure (normogonadotropic hypogonadism)
• Obstructive: CFTR • Acrosome defect: ACR, HRB, ADAD1, ADAM2, ADAM3, *etc* • Miscellaneous: Gpr64, ADGRG2, Esr1, *etc*
Teratozoospermia
• Globozoospermia: SPATA16, DPY19L2, PICK1, HRB, Csnk2a2, *etc* • Large head, multiple tails: AURKC • Tail defect: Ros1, TEKT2, PACRG, *etc* • Abnormal morphology (undefined): PMS2, HOOK1, Ixr, *etc*
Asthenozoospermia
• SLC26A8, DNAI1, DNAH1, POLL, AKAP4, SMCP, Nsun7, ADAD1, CRISP2, PACRG, LRRC6, GAPDS, *etc*
Astheno-terato-oligozoospermia
• CATSPER1, CATSPER2, SEPT12, KLHL10, NANOS1, TEKT2 (tail bending), SPAG16, SPAG6, CSTF2T, RBMXL2, Rsn, STRC, SPEM1, apoer2, Sept4, Cd59b, *etc*

to synthesize new strand of DNA complementary to the template strand. The PCR reaction generates copies of the target sequence exponentially. SNP microarray is carried out using commercially available DNA/SNP arrays (Illumina, Affimetrix, Agilent, etc) and interpretation is based on optical intensity. Here only the test DNA is labeled with flurochrome and its incorporation is proportionate to optical intensity (more the incorporation greater will be the optical intensity). In contrast, array comparative genomic hybridization (CGH) utilizes relative incorporation of probes (labeled test DNA vs. normal control DNA) on known DNA spots (instead of normal metaphase spread, as with CGH). This utilizes DNA hybridization principle i.e., more the initial DNA more will be the incorporation. Hybridization image is captured on specific scanner and primary data is analyzed using system specific softwares. Resolution is preferably set as 0.1 mb for CNVs whereas 5 mb is set for loss of heterozygosity (LOH). Secondary analysis of CNV may be carried out by web database resources viz., DECIPHER, OMIM, Gene, GeneCards, etc and compared with normal control databases &/or control sample data. Epigenomic microarray (Illumina 450K infinium methylation bead array) may be used to study epigenomic abnormalities. DNA methylation is measured using bisulfite-converted genomic DNA. After bisulfite treatment, unmethylated cytosine bases are deaminated to uracil, while methylated cytosine bases remain unchanged. The assay interrogates these chemically differentiated loci using one or two site specific probes (bead types) per CpG locus. The level of methylation for the interrogated locus is determined by calculating the ratio of the fluorescent signals from the methylated vs. unmethylated sites. It covers 96% of CpG islands, with multiple sites within islands and island shores, as well as island shelves. To assess the overall functionality of the individual CpG assays on Human Methylation 450, three human genomic DNA methylation reference standards viz., unmethylated (U, 0%), hemi-methylated (H, 50%) and methylated (M, 100%) controls are used. Software are used to analyse data and view results as heat maps, scatter plots,

and line plots besides information on chromosomal coordinates, percent GC, location in a CpG island, and methylation β values. Long non-coding RNAs (lncRNAs) are conserved, longer than 200 nucleotides non-coding RNA molecules. LncRNAs are important regulators for diverse functions and are involved in cellular functions, including epigenetic silencing, transcriptional regulation, RNA processing and RNA modification. LncRNAs are associated with human diseases such as cancers, Alzheimer's disease, heart diseases, etc. LncRNAs microarray is used to profile lncRNAs along with the entire set of protein-coding mRNAs. The lncRNA data analyses and annotation softwares unravel the complex lncRNA biology and regulatory relationships with the protein coding genes. Next generation sequencing (NGS) can be used for chromosomal analysis (including identification of balanced translocation using long read methods) as well as mutations in genes. It uses massively parallel whole genome sequencing or targeted sequencing (selected chromosomal regions of interest or gene panels) or SNP based targeted sequencing. Massively parallel sequencing usually covers whole genome and gives information on all chromosomes & sub-chromosomal regions or genome. Targeted sequencing covers few chromosomal loci or panel of genes and hence less informative. SNP sequencing is highly sensitive & specific for chromosomal analysis; can also detect triploidy, uni-parental disomy, maternal contamination besides microdeletion syndromes and specific gene mutations.

Based on prevalence data routine karyotyping of infertile men with unexplained spermatogenic failure is widely recommended for finding etiology as well as before going for ART. Sperm FISH is also commonly used to determine the proportion of aneuploidy present in sperms of infertile men with oligospermia, teratospermia, testicular/ epididymal sperms, etc. Testicular sperm from men with nonobstructive azoospermia display higher rate of aneuploidy in spermatozoa than ejaculated sperms. Sperm aneuploidy test (FISH) is indicated in oligospermia, nonobstructive azoospermia (testicular sperm), teratozoospermia, necrozoospermia, Klinefelter's syndrome (mosaic and nonmosaic), translocations, exposures to gonadotoxins, chemotherapy, pesticides exposure, repeated ART failures, etc. Sperm chromosomal study (FISH) aids counseling regarding PGD or alternative reproductive options. Y chromosome microdeletion/AZF deletion study is also indicated in non-obstructive azoospermia and oligospermia. Testing of AZF deletions has a prognostic impact for sperm extraction, since no sperm can be retrieved in AZFa deletion, while there is a fair chance of retrieving sperm in AZFc deletion.

Sperm chromatin compaction is increased twenty-fold compared with somatic cells following the replacement of 90–95% of histones in the sperm genome by the highly negatively charged nucleoproteins, protamine. Integration of protamine 1 and protamine 2 into the sperm genome during the elongation phase of spermatogenesis (in particular spermiogenesis) normally occurs in a strictly controlled 1:1 fashion. Significant deviations in the ratio have been associated with alteration in motility, morphology, and fertilization capacity as well as increased DNA fragmentation (130). Sperm DNA integrity is associated with semen characteristics and has an influence on fertilization, embryo quality and pregnancy outcome in conventional IVF. Sperm DNA integrity is disturbed in male genital infection, oxidative stress, exposure to pollutants, etc. At present, the results of sperm DNA integrity testing alone do not predict pregnancy rates achieved through natural conception (130).

Monogenic disorders associated with male infertility are Kallmann syndrome, Laurence Moon Biedl syndrome, Prader Willi syndrome, Noonan syndrome, androgen receptor mutations or trinucleotide expansion, FSH/LH (luteinizing hormone) receptor mutation, mitochondrial gene defects, etc and tests for detecting these mutations may be offered in specific cases. CNVs have not yet been defined as a cause of male infertility, but that seems inevitable. Link between epigenetics and male infertility involves protamine packaging of the sperm genome. However, it is clear that homozygous mutations in key epigenetic regulators affect male fertility. For couples failing multiple attempts at IVF/ICSI, additional testing with sperm FISH may be advised as elevated sperm aneuploidy rates have been observer among couples with repeated ICSI failures (131).

7. MANAGEMENT

Generally, patients are categorized into three groups. First group includes patients who can be diagnosed and treated by existing technology, for example, patients with hypogonadotropic hypogonadism. Unfortunately, this group is the smallest. Second group includes patients who can be diagnosed, but cannot be treated by existing technology, such as patients with primary testicular failure having AZF microdeletions or chromosomal aneuploidy (Klinefelter syndrome) as underlying cause of infertility. Third group includes patients who can neither be diagnosed nor treated. Majority of male infertile patients fall in this group. It is probable that knowledge of the underlying genetics may improve treatment options. Finally, the ultimate goal will be direct correction of underlying genetic defects (132).

Pre-testicular failure or hypogonadotropic hypogonadism (example Kallmann's syndrome) can be treated by pulsatile infusion of GnRH with a portable minipump or alternatively by HCG and FSH (preferably

by recombinant FSH/rFSH & recombinant HCG/rHCG). In view of the length of the spermatogenetic process, the treatment should be continued until spermatozoa appear in the ejaculate, which may take even one year (133).

Genetic abnormalities associated with the disorder are usually inherited and transmitted to offspring when patients opt for assisted reproduction; hence genetic counseling should be provided to patient once genetic etiology is detected. It is important to investigate idiopathic cases at genomic and epigenomic levels to find out the underlying causes. In azoospermic men with focal spermatogenesis or hypospermatogenesis or late maturation arrest, pregnancies can be achieved with testicular sperm extracted and injected into mature oocytes by ICSI. Similarly, *in vitro* spermatogenesis of germ cells obtained by testicular biopsy in these cases may result in pregnancy & live birth in near future.

In general, primary testicular failure of genetic/idiopathic origin is associated with very poor fertility even with assisted reproductive technologies. Currently there is no therapy for primary testicular failure with complete germ cell aplasia. Management of primary testicular failure involves avoiding risk factors as preventive measure &/or early diagnosis along-with early appropriate preventive management. Early management of varicocele &/or cryptorchidism may result in restoration of fertility. The risks arising from chemotherapy, radiation or surgery can be minimized by judicious planning and adopting preventive measures (care during surgery, prior cryopreservation of gamete/ gonadal biopsy and following protective measures during radiotherapy). Infertility is an undesirable side effect of oncotherapy. Currently semen sample banking is suggested to cancer patients prior to cancer treatment. However sperm banking is not possible for pre-pubertal boys. In such cases, testicular tissue banking is advocated prior to oncotherapy to achieve biological parenthood later in life, if the patient survives (134,135). The testicular biopsies are preserved either as intact small pieces or as cell suspension comprising germ cells. In future, the cell suspension can be transplanted into the seminiferous tubules or testis tissue pieces could be grafted at heterotopic sites to obtain sperm for assisted reproduction or spermatogonial stem cells can be matured *in vitro* to produce sperm. Germ cells transplantation leading to birth of mouse pups has been reported (136,137). An alternative approach to germ cell transplantation is to xenograft testicular tissue biopsy (with intact somatic environment) in immuno-deficient mice (138). This approach has resulted in complete spermatogenesis and sperm production from newborn mice, pigs and goats testicular grafts transplanted in nude mice (139). At present, it is suggested that we should bank prepubertal gonadal tissue of cancer patients prior to treatment that may help them restore fertility later using assisted reproduction although use of cryo-preserved testicular tissue to restore spermatogenesis is not yet established in human. Embryonic stem cells or induced pluripotent stem cells also can be differentiated *in vitro* to produce sperm. Various publications discussed in depth on artificial gametes and suggested that the use of artificial gametes to treat infertility will take some more time to come into practice (140–142).

Recent studies have shown that a novel population of pluripotent stem cells termed very small embryonic-like stem cells (VSELs) exists in normal and azoospermic human testes. Studies on mice show that VSELs survive cancer therapy because of their quiescent nature and can be isolated from chemo-ablated testis and undergo spermatogenesis when healthy niche (Sertoli or mesenchymal) cells are directly transplanted into the chemo-ablated testis. Several groups have reported beneficial effects and live births on transplanting mesenchymal cells in chemo-ablated rodent/mouse testes (143–146). VSELs may also be isolated from bone marrow and can be differentiated into germ cells (147). If this is true then there may be no need to even discuss fertility issues with cancer patients. There may not be a need to even wait till the individual wishes to plan his family. An early transplantation of mesenchymal cells may restore gonadal function and may help in achieving better secondary sexual development and avoid hormone replacement therapy, which is currently practiced to manage development and growth issues of cancer survivors. It is also worth experimenting using VSELs and mesenchymal cells (bone marrow derived) in primary testicular failure of genetic origin to restore fertility.

Predictive genomic medicine will help in identifying individual who are at risk of having non-obstructive azoospermia in future and will give them time to plan for gonad cryopreservation/ gamete cryobanking or use of stem cells viz., VSELs in order to counter future problems. Most cases of primary testicular failure of genetic etiology are presented as normal spermatogenesis in younger age group however spermatogenesis decreases rapidly over a period of few years after puberty indicating accelerated programmed death of germ cells. In future predictive medicine approaches will identify these cases and appropriate preventive measures may be instituted before complete testicular failure occurs.

8. IMPORTANCE OF EXPLORING GENETIC BASIS OF MALE INFERTILITY

The advent of ART such as ICSI allows men with suboptimal sperm quality (often associated with genetic defects) to produce a child of their own. This ART procedure may lead to the transmission of genetic defect and possibly additional epigenetic modifications from *in*

vitro manipulation to the embryo, which may affect future generations. At present, there is no definite evidence of significant increase in imprinting disorders (148) or aneuploidy of sex chromosomes (from 0.2% to 0.6%) and autosomes (from 0.07% to 0.4%) associated with ART procedures (149). However, it is our responsibility to find out the underlying genetic etiology of male infertility in order to prevent transmission to offspring for example, transferring chromosomally normal embryo (through preimplantation genetic diagnosis) in Klinefelter syndrome. In general, Klinefelter syndrome male is believed to be sterile, but it has been estimated that 25% of non-mosaic and over 70% mosaic Klinefelter syndrome males have sperm in their ejaculate (2,13) in younger age. These patients have chance to father a normal pregnancy using ICSI (as number of sperms are few) and preimplantation genetic diagnosis (which will help in selecting euploid embryo from large number of aneuploidy embryos being formed due to high frequency of aneuploid sperms) (150,151). Preimplantation genetic diagnosis should be performed before embryo transfer to ensure that the offspring is not aneuploid (148). Similarly, male infertility due to Yq microdeletions (AZFa,b,c) are common and can be managed by ART, in particular ICSI procedure. Here, it is essential to know that Yq microdeletions will pass on to all male offspring hence it is essential to discuss these issues with couple before going for ART (152). Alternatively, female zygote (confirmed by preimplantation genetic diagnosis) may be used to achieve pregnancy leading to birth of healthy female child.

9. HOW TO PREDICT AND PREVENT MALE INFERTILITY USING GENOMICS?

Traditionally it is believed that genetic disorders are untreatable. Now this concept is changing. The major contribution of genetics is to predict and prevent a disorder thus decreasing its burden right from the planning of reproduction. Genetic factors are greatly responsible for infertility, pregnancy losses, malformation and cancer. The ideal time to apply genetics should be from the time of gametogenesis to peri-conception period so that prediction and/or prevention (primary and/or secondary) is possible. Advances in molecular technologies (NGS and microarray) as well as reproductive technologies (preimplantation genetic diagnosis/PGD, assisted reproductive technology/ART, etc) have increased this drive and expectations. Rapid dissemination of information in media has affected daily reproductive care so much that an understanding of genetics is essential for all reproductive specialists, in particular how to predict and prevent a disorder. This would be of much use to young cancer patients wanting to father a child in future as their survival rate is increasing. Genetics is becoming more important following the development of *in vitro* fertilization (IVF) and intra cytoplasmic sperm injection (ICSI) as these procedures lead to more genetic as well as epigenetic abnormality in offspring. The use of ICSI has raised major concerns about safety of the offspring, since it bypasses the physiological protective mechanisms related to normal fertilization. Natural selection prevents the transmission of mutations causing infertility. This protective mechanism is bypassed in ART. The risk for genetic causes of infertility thus will increase in future generations conceived through ART (153), if no preventive measures adopted.

Advances in reproductive technology like cellular reprogramming or cellular differentiation or dedifferentiation have created another dimension in reproduction. Now, in the laboratory stem cell can be manipulated to become specialized cells and can be used to treat disease. Embryonic stem cells can be differentiated into gamete (sperm or oocyte) to treat infertility. Recent progress in germline stem cell isolation and culture may provide a platform for *in vitro* gamete development and may open a new era of gametogenesis in a dish and personalized infertility treatment in coming years (144,154). For therapy with stem cells, the issue of immuno-compatibility arises. The breakthroughs in somatic cell nuclear transfer have raised the possibility of generating unlimited sources of undifferentiated cells, with potential applications without immune rejection. However, all these procedures will lead to transmission of underlying genetic cause as well as likely additional epigenetic problem into offspring which will require specific counseling and preventive strategy.

The genomic screening technology has enabled the detection of genetic etiologies (chromosomal abnormalities, Yq microdeletion, CNV, gene mutation, etc) implicated in male infertility. This creates opportunities for the development of more precise and early detection, even at preimplantation or prenatal or neonatal or childhood stage. The growing possibility of infertility prediction may make prevention and early precision treatment a reality. It is also likely that epigenetic profiling of spermatozoa from infertile men may be useful in the near future, including assessing the potential of the spermatozoa to contribute to normal embryogenesis and in assessing risks associated with environmental exposures (155).

Once genomic technologies (DNA microarray and/or NGS) are in use for screening genetic etiologies (testicular, pre-testicular, post-testicular or combinations gene panels; Table 6) of male infertility as part of predictive medicine practice, high-risk groups may be identified before development of disease and appropriate measures may be started much before the pathology appears. Cases like Klinefelter syndrome, Yq microdeletion, hypogonadotropic hypogonadism, etc where pathology manifests after puberty may benefit in future through predictive genomic medicine

practice (prediction before disease manifestation followed by preventive measures like gonad/gamete cryopreservation & use later when required through *in vitro or in vivo* gametogenesis or treating with deficient hormones in hypogonadotropic hypogonadism). It is possible to construct a logical screening program of genes panel for mutation, chromosomes abnormalities, CNVs and Yq microdeletions causing infertility. However, there are many unknown etiologies are involved in the control of spermatogenesis. Identification of these unknown factors may open up newer avenues for therapeutic and diagnostic approaches. With the better understanding of the underlying cause of male infertility as well as continued advances in genomics and epigenomics, it is likely that the hope of personalized medicine in male infertility will be realized in coming years and personalized genomic approaches to predict, prevent and manage male infertility will improve our ability to care infertile couples.

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