Abnormalities are likely to be present, but are not detected by conventional approaches. Genetic defects may be partly or entirely involved in the true cause of infertility in such men. Since assisted reproductive technology (ART) is overall successful regardless of the underlying infertility cause, this is often the next step for many couples with unexplained infertility. However, genetically compromised spermatozoa used in ART have been associated with a wide range of adverse outcomes including abnormal embryo development that may either fail to implant or result in an increased risk of miscarriage and defects in the offspring. Therefore, it is sound to determine the origin of the problem to allow appropriate counseling and management.

In this review, I first discuss the genetic disorders associated with UMI and then, I outline the testing performed to diagnose genetic conditions associated with UMI. Finally, I propose a workable plan for genetic evaluation of men with unexplained infertility and discuss the future perspective.
Chromosomal translocations occur in males with unexplained infertility (UMI), accounting for 2.1-15.5% of cases. Abnormalities in infertile males, including chromosomal defects, can be either balanced or unbalanced; most often they are either associated with severe sperm abnormalities or lethal for fetuses. Robertsonian translocation (RT), however, may account for few cases of unexplained infertility.

**REVIEW CRITERIA**

An extensive search of studies examining the relationship between genetics and UMI was performed using search engines such as ScienceDirect, OVID, PubMed and MedLine. The overall strategy for study identification and data extraction was based on the following key words: “Genetics,” “epigenetics,” “unexplained infertility,” “male infertility,” “diagnosis,” “infertile men,” “sperm parameters,” “pregnancy rate” and the specific genetic tests. Articles published in English only were considered. Data that were solely published in conference or meeting proceedings, websites or books were not included. Websites and book-chapter citations providing conceptual content were used.

**GENETIC DISORDERS IN UMI**

Spermatogonial series are kept in a latent state inside the fetal testis until puberty when they increase in number by repeated mitotic divisions. Spermatogenesis starts in adolescence and is controlled by genetic factors. It has been estimated that 2000 genes are essential for the full process to be completed; of these, only 30 genes are present in the Y chromosome.[12,13]

Genetic abnormalities including chromosomal aberrations and monogenic diseases have been estimated to respond in 10-15% of infertility cases.[13] Infertile men with genetic alterations usually present with impaired spermatogenesis, genital structural abnormalities, reduced testicular size, hypogonadism and sperm dysfunction.[14] Although its prevalence is unknown, genetic abnormalities may also occur in males with UMI.[10-18]

Didactically, genetic abnormalities can be grouped into four main categories: (i) Chromosomal defects in the somatic cells; (ii) gene mutations and polymorphisms in the somatic cells; (iii) sperm chromosomal abnormalities; and (iv) epigenetic disorders. Although the first two categories affect men with abnormal genotypes in somatic cells, sperm chromosomal abnormalities can be originated from individuals with either abnormal or normal genotypes. Epigenetics, on the other hand, refers to the mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in deoxyribonucleic acid (DNA) sequence.

**Chromosomal defects**

Chromosomal defects are the most common genetic abnormalities in infertile males, accounting for 2.1-15.5% of cases.[16] Klinefelter syndrome, chromosome translocations, inversions and deletions fall in this category and the vast majority of affected individuals display severely compromised semen quality. Translocation carriers, however, may have varying sperm production phenotypes ranging from normal spermatogenesis to inability to produce spermatozoa.[17] Chromosomal translocations occur when non-homologous chromosomes exchange segments. Translocations involving the sex chromosomes and autosomes can be either balanced or unbalanced; most often they are either associated with severe sperm abnormalities or lethal for fetuses. Robertsonian translocation (RT), however, may account for few cases of unexplained infertility.[18]

RT represents a translocation category in which two acrocentric chromosomes fuse at the region next to the centromere causing loss of their short arms. The resulting balanced karyotype has only 45 chromosomes including the chromosome with the translocation, which is actually constituted by long arms of two chromosomes. As the short arms of the five acrocentric chromosomes (chromosomes 13, 14, 15, 21 and 22) harbor multiple copies of ribosomal ribonucleic acid (RNA), loss of their short arms is not harmful. RTs are the most frequent structural chromosome abnormalities in humans, affecting the fertility status of one in 1000 men.[19] Despite being estimated to 0.8% in subfertile males, its prevalence is nine times higher than the general population.[20] In heterozygous carriers, RT chromosomes and their acrocentric homologs may undergo either alternate segregation or adjacent segregation at meiosis. Alternate segregation results in the formation of balanced gametes carrying either RT or a normal karyotype, whereas adjacent segregation leads to the formation of aneuploid gametes. Carriers of RT may exhibit normal phenotype but otherwise be infertile due to more or less severe sperm abnormalities.[21] There is also a risk of unbalanced gamete production that results in an increased risk of spontaneous abortion and unbalanced offspring. The most relevant clinical aspect involves the carriers of translocations in chromosome 21 as they are at risk of producing a child with Down Syndrome due to a 21q trisomy inheritance.

**Gene mutations**

Like chromosomal defects, gene mutations are usually related to severely abnormal sperm production phenotypes. Microdeletions in the Y chromosome Azoospermia factor region, mutations in the cystic fibrosis gene and mutations and polymorphisms of the androgen receptor gene are classic examples of genetic abnormalities in this disease category.[14,16] Abnormalities of interest in UMI include mutations of cation channel of sperm (CatSper) and sperm mitochondrial genes. The diagnosis of gene mutations can be made only by molecular genetic testing.
In humans, the extension of hyperactivated motility in a sperm population is positively correlated with the extent of zona pellucida binding, acrosome reaction, zona-free oocyte penetration and fertilization capacity in vitro. An abnormally low proportion of sperm exhibiting hyperactivation was found in UMI associated with CatSper1 gene mutations. In mice, mutations in CatSper 1-4 ion channel proteins lead to infertility despite normal semen and testicular development. CatSper-related male infertility is inherited in an autosomal recessive manner. CatSper1 mutations can be identified by sequencing analysis and testing is clinically available. In summary, mutations in the CatSper channel genes can be considered a potential cause in UMI.

Sperm mitochondrial deoxyribonucleic acid mutations
Sperm mitochondria are located around the mid-piece in a helical arrangement containing 1-2 mitochondrial deoxyribonucleic acid (mtDNA). Mitochondrial DNA encodes 37 genes that regulate oxidative phosphorylation. It differs from nuclear DNA in respect to replication, repair mechanism, genome packing and position. Unlike nuclear DNA, mtDNA is not protected by histones and physically associates with the inner mitochondrial membrane, where highly mutagenic oxygen radicals are generated by the respiratory chain. The leakage of these free radicals makes mitochondria a major source of reactive oxygen species and may also explain why mtDNA is more prone to mutations than nuclear DNA.

Mitochondrial DNA polymerase gamma (POLG) is a key enzyme involved in the elongation and repair of mitochondrial DNA strands that encode for the POLG gene. Studies have shown an association between POLG gene polymorphisms and UMI. Polymorphism of this gene might decrease sperm oocyte penetration and fertilization even when sperm parameters were normal. In one study, 14.3% of men with unexplained infertility had POLG gene polymorphisms compared with only 2.3% in the unselected control group and 0.9% in fertile controls. Despite the yet undefined role of determining mtDNA mutations in UMI, this information may prove beneficial when recommending infertile couples for ART. POLG gene mutations can be detected using sequence analysis and testing is clinically available (www.transgenomic.com). Of note, prognosis for pregnancy is good in cases treated with ART since mtDNA is not transmitted to the offspring.

Sperm chromosomal abnormalities
A threefold increase in the frequency of sperm aneuploidy is found in infertile men (around 3%) compared with fertile counterparts. Sperm aneuploidy has been associated with severe sperm defects, unexplained infertility, recurrent miscarriage, in vitro fertilization (IVF) failure and increased risk of chromosome abnormalities in newborns. In fact, sperm aneuploidy has been associated with paternally derived de novo chromosome abnormalities in embryos, fetuses and newborns conceived after intracytoplasmic sperm injection (ICSI). Such abnormalities occur in 2-3% of ICSI conceptions, which is three times greater than natural conceptions. Although not a first-line investigation, measurement of chromosomal abnormalities in sperm may be indicative in selected cases of UMI.

Epigenetic disorders
Epigenetics applied to male infertility refers to all types of molecular information that are transmitted from the spermatozoa to the embryo. The epigenetic regulatory mechanisms required for proper embryogenesis include: (i) Functional role of centrosome; (ii) DNA methylation; (iii) histone modifications; (iv) chromatin remodeling; and (v) role of RNA transcripts and telomere length. Methylation is the best example of the sperm epigenetic contribution to the embryo as human embryos cannot develop unless paternal methylation is normal. DNA methylation is referred to as ‘imprinting’, and it determines, which genes from both parental and maternal genomes will be expressed in the embryo. DNA imprinting regions are reset at every reproductive cycle thus allowing renewing of parental imprints in parental germ cells. Activation of imprinting is a result of differential marking of DNA regions with histone modifications, methylation, or a combination of both, to allow only one allele to remain active. Methylation occurs at the 5-carbon position of cytosines found in cytosine-phosphate-guanine dinucleotides (CpGs). CpGs are found in high concentrations near the gene promoter and are termed “CpGs islands”. Decreased methylation of the paternal IGF2/H19 imprinting control region 1 (ICR1) and GTL2 have been found in spermatozoa of men with disturbed spermatogenesis. The degree of methylation in the IGF2/H19 ICR1 and mesoderm-specific transcript locus has been also associated with infertility. Histones also play an important role in the transmission of paternal epigenetic information. Histone covalent modifications are associated with several nuclear functions including transcriptional control, chromatin packaging and DNA methylation. During chromatin packaging,
85% of histones are replaced by protamines. In an intermediate phase of the replacement process, transitional proteins (TP) are inserted into the chromatin structure. In mice, disruption of TP1 and TP2 encoding genes can produce infertile phenotypes, as well as unbalanced protamination ratios and early transcription of mRNA. Histones are more easily extracted from DNA than protamines and histone-bound DNA is more susceptible to DNA-damaging agents than protamine counterparts. If abnormally modified, histones are candidates for impeding normal embryogenesis. Finally, telomeres have also been targeted as potential candidates to explain some infertile phenotypes. Its functions include protection of the genetic information encoded on the chromosome, localizing the chromosomes in the nucleus and supporting DNA replication. Abnormal shortening of telomeres has been associated with male factor infertility. Studies in mice have suggested that there is a protective mechanism which degrades spermatocytes with reduced telomere length to prevent their maturation. If this process failed, spermatocytes with shortened telomeres would reach meiosis I, which is indicative they cleared this checkpoint without being degraded. Despite these considerations, the role of telomere length in male infertility remains to be further investigated.

In summary, variations in the sperm epigenome may also contribute to male fertility by DNA protamination and methylation. It means that a series of epigenetic signals coming from the paternal chromatin are needed for the proper execution of the DNA-encoded genetic program. Genetic inheritance is thus much more complex than the transmission of the information provided exclusively by the paternal DNA.

**GENETIC TESTING IN UMI**

A series of tests can be used to identify genetic and epigenetic defects in UMI [Table 1]. At present the most common test used to evaluate the genetic status of such men is the cytogenetic analysis by karyotyping. Since the incidence of karyotype anomalies is inversely proportional to sperm concentration, abnormal results are found in less than 1% in UMI. Karyotyping involves the collection of heparinized peripheral blood samples and the isolation of a plasma lymphocyte suspension. Lymphocytes are cultured to promote mitotic stimulation and then division is arrested at the metaphase. A dye, often Giemsa (G-banding), is used to stain bands on the chromosomes. With the use of light microscopy to evaluate the appearance of chromosomes, karyotyping resolves variations in the DNA complement of ≥4 Mb. Structural chromosome abnormalities such as translocations can be easily detected by cytogenetic techniques.

### Table 1: Genetic tests in unexplained male infertility

| Test | Principle | Specimen tested |
|------|-----------|-----------------|
| Cytogenetic test (karyotype) | Assess number and appearance of eukaryotic cells | Peripheral blood |
| Gene sequencing for mutational and polymorphism analysis | Determine gene sequencing and mutation occurrence using dye terminator sequence | Peripheral blood |
| Fluorescence in situ hybridization | Detect chromosomal aneuploidy and structural abnormalities both in eukaryotic cells and spermatooza | Peripheral blood; sperm |
| Microarray technology | Analyze copy number variations, gene expression levels, single nucleotide polymorphisms and mRNA transcripts pool expressed by sperm | Sperm |
| Next-generation sequencing technologies | Detect DNA methylation problems | Peripheral blood |

For specific gene sequencing and mutational analyses, the “dye terminator sequence” method is usually performed. It also involves the collection of peripheral blood. Its principle is the premature termination of four separate sequencing reactions that contain all standard deoxynucleotides (Desoxyadenosine triphosphate [dATP], Desoxyguanosine triphosphate [dGTP], Desoxyctydine triphosphate [dCTP] and Desoxythymidine triphosphate [dTTP]) and the DNA polymerase. Only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP), which are chain-terminating nucleotides that lack the 3’-OH group required for the formation of a phosphodiester bond between two nucleotides, is added to each reaction. Thus, DNA strand extension is terminated, resulting in DNA fragments of varying lengths. Next, these labeled DNA fragments are separated by gel electrophoresis on a denaturing polyacrylamide-urea gel and read in a specific manner from the shortest to the longest.

High resolution assessment of sperm genetic complement can be achieved using fluorescence in situ hybridization (FISH). It combines the classic karyotype method with molecular techniques using fluorescent DNA probes to bind selectively to a specific genetic sequence after denaturation. The fluorochromes are then visualized with the use of fluorescent microscopy. FISH can be used to detect chromosomal aneuploidy and structural abnormalities both in eukaryotic cells and sperm. Unlike karyotype that requires metaphase cells, FISH can be applied to interphase nuclei. Studies from the last decade using FISH on sperm showed that the rate of sperm aneuploidy was inversely correlated to sperm quality. The incidence of sperm disomy (two pairs of a single
chromosome), diplody (two pairs of all chromosomes) and polyplody are also positively correlated to the occurrence of sperm morphology abnormalities including macrocephalic, multinucleate and multiflagellate sperm.\[^{49,50}\] FISH of sperm is most often used in cases of recurrent miscarriage as it defines meiotic defects in the form of aneuploid sperm.\[^{51}\]

The survey of sperm epigenome is carried out with the use of next-generation sequencing technologies. Bisulfite sequencing (Bi-seq), reduced-representation Bi-seq, methylated DNA immunoprecipitation sequencing, methylated DNA capture by affinity purification sequencing, methylated DNA binding domain sequence and ethylation-sensitive restriction enzyme sequencing are the methods for detecting DNA methylation problems. Chromatin immunoprecipitation followed by sequencing is the standard approach used to detect histone-tail modifications while long non-coding RNAs can be detected using RNA-sequencing studies.\[^{52}\]

CURRENT SCENARIO AND FUTURE PERSPECTIVES FOR THE GENETIC DIAGNOSIS IN UMI

Genetic testing not only allows clarifying an obscure infertility diagnosis, but also helps to prevent miscarriage and iatrogenic transmission of genetic defects to the offspring by ART. The most important strengths of genetic testing lie in its ability to identify men with genetically defective sperm thus aiding couples make informed reproductive decisions. In the past, only large structural chromosomal aberrations, defined by karyotype analysis, were detected. Using modern testing much smaller genomic regions has been found to be responsible for infertility. In fact, current estimates indicate that genetic abnormalities cause 15-30% of male factor infertility.\[^{19}\]

Despite being limited by the widespread use of ART, a cost-effective genetic evaluation should be considered as an integral part of the work-up plan in UMI. Given the simplicity and low-cost of karyotype analysis, the test might be offered as a first-line investigation in cases of UMI, especially after ART failure or recurrent pregnancy loss. Although not a first line investigation, sperm aneuploidy assessment might also be considered in cases of UMI associated with IVF failures or recurrent pregnancy loss.

At present, the routine use of specific gene sequences, mutation analysis and sperm epigenome survey are limited by several factors including cost, availability, clinical relevance and endorsement by societies’ guidelines. In the near future, however, novel platforms that have the potential to redefine how male infertility is diagnosed are likely to become widely available. Microarray technology, which evaluates for copy number variations, gene expression levels and single nucleotide polymorphisms, has yielded several male fertility gene candidates with strong association with infertility and sperm quality and function.\[^{53-56}\] An example of its application is the array comparative genomic hybridization to assess the relative quantities of DNA between samples, which allows to determine gene copy number as a function of chromosomal location.\[^{48}\] In a recent study, the genetic sperm expression profile was used to classify the fertility status of men with normal sperm parameters based on the expression signature of four genes (EIF5A, RPL13, RPL23A, RPS27A). The authors found that such analysis was able to predict the chances of pregnancy in intrauterine insemination with sensitivity and specificity of 82% and 90%, respectively.\[^{57}\] Microarray technologies have also enabled evaluation of sperm messenger RNA that correlate with spermatogenesis, sperm motility, germ cell antiapoptotic processes, DNA repair, oxidative stress reduction and histone modification.\[^{54,58-61}\] Recent investigations have shown that the mRNA profiles differ in sperm that succeed or fail to result in pregnancies in ART.\[^{59,60,61}\]

Concerning sperm epigenetics, there is still a lot to be learned but this field bears the promise of reversing the effect due to its dynamic nature. Unlike genetic studies, a deeper understanding of the epigenetic processes could shed light on therapies based on epigenome modifications.

CONCLUSIONS

Male fertility, including spermatogenesis and sperm function, is regulated by thousands of genes. As men with unexplained infertility can harbor genetic abnormalities that may compromise their reproductive potential, efforts should be made to identify such conditions. Currently, few diagnostic tools are available for routine use and their usefulness is not yet completely clear. Chromosomal abnormalities in somatic cells can be detected by karyotyping. Sperm aneuploidy assessment in couples with unexplained infertility experiencing either repeated IVF failures or recurrent pregnancy loss can be performed by FISH while mutations and polymorphisms are identified by specific gene sequencing and mutational analysis methods. Many advances are currently being made and the use of novel genetic microarray technology may hold the key to more accurately diagnosing and treating men with unexplained infertility.

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