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A Review :

MITOCHONDRIAL DNA MUTATIONS (DYSFUNCTION) AND MALE INFERTILITY

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ABSTRACT

The male factor is at least partly responsible in about 50% of infertile couples. The diagnosis of male infertility has been primarily based on the traditional semen analysis. Traditionally, genetic analysis for infertility has been based at the chromosomal level. Further, in order to explore the causes of the unexplained infertility, there are several candidate genes that are being studied that could lead to future breakthroughs. However, one area of genetic investigation, which has largely been ignored by reproductive biologists until recently, is the role of the mitochondrion and its genome. Mitochondria have profound effect on every biochemical pathway including the one that drives the sperm motility. The human mitochondrial DNA (mtDNA) is a double stranded, closed circular molecule, 16,569 bp in length which contains 37 genes coding for 13 proteins, 2 rRNAs and 22 tRNAs which are essential components of four respiratory enzyme complexes. In the past few years, more than 24 mutations of mtDNA have been identified and proved to be associated with human diseases. About 85% of sperm samples contained large-scale mtDNA deletions of variable sizes and that most spermatozoa had 2 to 7 deletions of mtDNA. Among the mitochondrial deletions observed, the so-called "common deletion" of 4977bp was the most prevalent and abundant one. mtDNA mutations can be detected with the aid of MITOMAP database and Mitoanalyser software. The mtDNA mutations detected so far may just represent the "tip of the iceberg" of all possible mutations in spermatozoa. Since sperm require a substantial amount of energy to swim fast enough to reach the oviduct during fertilization, the appropriate bioenergetic function of mitochondria is critical for male infertility.

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Approximately 15% of couples attempting their first pregnancy meet with failure. Data available over the past twenty years reveal that in approximately 30% of cases pathology is found in the man alone, and in another 20% both the man and woman are abnormal. Therefore, the male factor is at least partly responsible in about 50% of infertile couples. In men, hormone disorders, illness, reproductive anatomy trauma and obstruction, and sexual dysfunction can temporarily or permanently affect sperm and prevent conception. Some disorders become more difficult to treat, the longer they persist without treatment.

The diagnosis of male infertility has been primarily based on the traditional semen analysis as outlined by The World Health Organization Guidelines (1999) with a strong emphasis on the assessment of semen volume and sperm concentration, motility and morphology. About 75 per cent of men who are infertile suffer from oligospermy, a very low sperm count, or from asthenozoospermia, a condition in which many sperm are immotile. Both conditions are untreatable and poorly understood. A group of researchers in Spain has found genetic variants that correlate with a sperm's ability to swim.

Traditionally, genetic analysis has been based at the chromosomal level. Further, in order to explore the causes of the unexplained infertility, there are several candidate genes that are being studied that could lead to future breakthroughs. Many studies indicated that the incidence of chromosomal abnormalities was correlated with the severity of male factor infertility but mainly related to sperm concentration. Multiple studies have been conducted to determine the incidence of Y chromosome microdeletions. Other genetic causes involve CFTR mutations, *DAZL* gene mutation on autosomal chromosome 3 and many more. However, one area of genetic investigation, which has largely been ignored by reproductive biologists until recently, is the role of the mitochondrion and its genome. Mitochondria have profound effect on every biochemical pathway including the one that drives the sperm motility. Sperm motility is heavily dependent on the ATP generated by oxidative phosphorylation in the mitochondrial sheath. This review pays particular attention to the role of the mitochondrion