Commentary

Protamines and their role in pathogenesis of male infertility

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Sperm DNA damage is the single largest cause of defective sperm function and may be the underlying cause of idiopathic male infertility. According to the WHO published data, male infertility contributes to about 45–50% cases of infertility (1). Male infertility is defined as a multifactorial syndrome affecting 1 out of every 20 men in the reproductive age group (2). Although extensive research has been done in the context of male infertility but the exact cause is still unknown (idiopathic) and is mainly attributed to genetic reasons (3). Decline in sperm function is believed to be the primary, single, and defined cause of male infertility, resulting in failed fertilization (4).

Mammalian sperm DNA shows six fold higher degree of compaction in comparison to the loose chromatin structure of somatic cells where the DNA is first packed into nucleosomes (5) and then into a solenoid (6). This hierarchical packaging increases the volume of chromatin in somatic cells because of the added volume of histones and central core of solenoid. However, such packaging is not possible in sperm chromatin as their nuclei do not possess the volume required for such level of DNA compaction.

Sperm nuclear genome is highly compacted and bound to sperm nuclear proteins called as protamines which are highly basic and the most abundant nuclear proteins in many species (including mammals) and act by extensive packaging of the sperm nuclear genome (7). The protamine gene family includes protamine 1 (PRM1), protamine 2 (PRM1) and transition protein 2 (TNP2) which together encompass a stretch of 13–15 kb of DNA on human chromosome 16p13.3. Protamines are highly basic nuclear proteins rich in arginine (40–70%) and cysteine (8–18%) which neutralise the charge on DNA and thus aids in its compaction. A single protamine gene is expressed in most mammals, but a second protamine gene is expressed in a few mammals, including mice and humans (8). PRM1 is encoded by a single-copy gene and the family of PRM2 proteins (PRM2, PRM3, and PRM4) are also encoded by a single gene. PRM1 is found in several species however, PRM2 is found in humans and few other mammals and data suggest a positive selection during evolution. Such a high level of condensation of the sperm nucleus aids in maintenance of the hydrodynamic shape, which aids both in sperm motility and its transit through the male and female reproductive tract and vital for maintenance of genomic integrity maintaining the epigenetic imprints (9). During later stages of spermiogenesis, majority of histones are replaced by transition proteins in the round spermatids which is then replaced by protamines i.e., protamine 1 (PRM1) and protamine 2 (PRM2) in the elongated spermatids and only 15% DNA retains the nucleosomal structure (10). The sperm genome is also partitioned into two compartments a peripheral histone bound compartment and a central compact crystalline toroid which is bound to protamines. Haploinsufficiency of either PRM1 or PRM2 (11) or abnormal PRM1/PRM2 protein ratio is associated with an increased risk of male factor infertility as this may result in improper compaction of sperm nuclear DNA and leaving the DNA highly vulnerable to environmental insults (12). Transgenic mice with altered expression of protamines present with infertility and have abnormal spermatozoa with several structural defects (13). Though there are several causes of DNA damage like oxidative stress, environmental pollutants, persistant organic pollutants,

electromagnetic radiation, infections, inflammation, varicocele, persistence of nicks post spermiogenesis and defective packaging of sperm DNA makes the sperm more vulnerable to damage (14,15).

A noticeable number of case-control studies have been done which have shown that polymorphisms or mutations in protamine encoded genes results in conformational changes in the encoded proteins, changes in sperm chromatin structure and hence impaired spermatogenesis. Polymorphism in PRM1 (rs35576928, rs35262993, rs737008) and PRM2 (rs2070923, rs1646022) is associated with an increased risk of male infertility however, the elemental cause behind this is still unknown (16,17).

A recent meta-analysis by Jiang *et al*., 2015 and colleagues was done to establish the correlation between the 6 common single nucleotide polymorphisms i.e., rs35576928, rs35262993, rs737008 in PRM 1 and rs2070923, rs1646022 in PRM 2 and an increased risk to male infertility. This meta-analysis was based on 13 previously published case-control studies, including 7,350 cases and 6,167 controls (18). In this meta-analysis, the authors reported no significant association between rs737008 and male infertility under the four genotype models. (CA *vs*. CC, AA *vs*. CC, AA + CA *vs*. CC and AA *vs*. CA + CC) whereas subgroup analysis showed significant association between rs737008 polymorphism and male infertility in subgroups of population based under the dominant model (for AA + CA *vs*. CC: OR 0.75; 95% CI, 0.57–0.97; P=0.030), while no such correlation was observed for the other subgroups, such as the Asian and the Caucasian group. The authors found significant association between rs2301365 and an elevated risk of male infertility under the four genotype models (AA + CA *vs*. CC: OR 1.32; 95% CI, 1.08–1.60; P=0.006; for CA *vs*. CC: OR 1.27; 95% CI, 1.04–1.56; P=0.022; for AA *vs*. CC: OR 1.66; 95% CI, 1.07–2.58; P=0.024; for AA + CA *vs*. CC: OR 1.53; 95% CI, 1.00–2.36; P=0.052; for A *vs*. C: OR 1.28; 95% CI, 1.09–1.51; P=0.003). For rs1646022, no significant association was found between rs1646022 and male infertility risk under the four genotype models studied (GC *vs*. GG, CC *vs*. GG, CC + GC *vs*. GG and CC *vs*. GC + GG) but significant association was observed between rs1646022 and an increased risk of male infertility in subgroups of Asians (CC + GC *vs*. GG: OR 0.68; 95% CI, 0.48–0.97; P=0.032). Meta-analysis of other SNPs i.e., rs35576928, rs35262993 and rs2070923 did not find any association with an increased risk for male infertility.

An increase in sperm histone:protamine ratio is associated with poor chromatin compaction and thus, male factor infertility (19). Altered relative ratio of PRM1:PRM2 at the level of mRNA and protein also leads to male factor infertility (20). Perturbation in PRM1:PRM2 is associated with poor chromatin and hence an increased risk of male infertility as sperm requires a full complement of both the protamines to convey the male genome to the next generation (21). DNA damage in sperm is only partially repaired due to highly truncated DNA damage detection and repair mechanism (22). Jiang *et al*. documented the protective role of rs737008 polymorphism of PRM1 and rs1646022 polymorphism of PRM2 as protective factors against Asian infertility (16).

In the present meta-analysis, the authors have documented no association between rs35576928 and male infertility risk but He *et al*., have reported that PRM1 variant rs35576928 (p.R34S) is associated with severely defective spermatogenesis in the Chinese Han population (23). Cho *et al*., have documented that deficiency of PRM2 leads to disruption of PRM1:PRM2 ratio, sperm DNA damage and ultimately embryo cell death in mice (11). Thus, for maintenance of sperm DNA integrity optimal PRM1 and PRM2 ratios should be maintained as DNA repair mechanism are deficient in sperm and this is vital for birth of healthy offspring. Thus, a detailed history should be taken to exclude all possible causes of DNA damage and in idiopathic cases with loss of sperm DNA integrity, it is important to analyse expression levels of PRM1 and PRM2 and analysis of pathogenic variants in genes encoding for these proteins.

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Footnote

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