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Association between promoter methylation of *MLH1* and *MSH2* and reactive oxygen species in oligozoospermic men—A pilot study

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Summary

MLH1 and *MSH2* are important genes for DNA mismatch repair and crossing over during meiosis and are implicated in male infertility. Therefore, the methylation patterns of the DNA mismatch repair genes *MLH1* and *MSH2* in oligozoospermic males were investigated. Ten oligozoospermic patients and 29 normozoospermic donors were analysed. Methylation profiles of the *MLH1* and *MSH2* promotors were analysed. In addition, sperm motility and seminal reactive oxygen species (ROS) were recorded. Receiver operating characteristic (ROC) analysis was conducted to determine the accuracy of the DNA methylation status of *MLH1* and *MSH2* to distinguish between oligozoospermic and normozoospermic men. In oligozoospermic men, *MLH1* was significantly (p = .0013) more methylated compared to normozoospermic men. Additionally, there was a significant positive association (r = .384; p = .0159) between seminal ROS levels and *MLH1* methylation. Contrary, no association between *MSH2* methylation and oligozoospermia was found. ROC curve analysis for methylation status of *MLH1* was significant (p = .0275) with an area under the curve of 61.1%, a sensitivity of 22.2% and a specificity of 100.0%. This pilot study indicates oligozoospermic patients have more methylation of *MLH1* than normozoospermic patients. Whether hypermethylation of the *MLH1* promoter plays a role in repairing relevant mismatches of sperm DNA strands in idiopathic oligozoospermia warrants further investigation.

1 | INTRODUCTION

Despite considerable efforts to determine the causes of male infertility, approximately 30% of these infertility cases are deemed idiopathic or unexplained (Groen et al., 2016). Recent studies have shown an association between idiopathic male infertility and epigenetic modifications, including promoter methylation in imprinted, reproduction-related and developmental genes in spermatozoa and might explain cases of idiopathic male infertility (Gunes, Arslan, Hekim, & Asci, 2016; Jenkins et al., 2016; Urdinguio et al., 2015).

The DNA mismatch repair (DMMR) mechanism is essential for maintaining cell genomic stability. DMMR proteins remove base substitution mismatches and insertion–deletion loops during replication and recombination. Mismatches occur during the DNA

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