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Computational Analysis of Nonsynonymous Single Nucleotide Polymorphisms in Human *AURKC* Gene Related to Male Infertility Phenotype

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ABSTRACT

Introduction: Male infertility is a complex multifactorial disease with highly heterogeneous phenotypic manifestations ranging from complete absence of sperm in the testis to distinct changes in sperm quality. Genetic defects are widely acknowledged to be a significant factor in the cause of idiopathic male infertility. Hence, identifying the genetic causes of male infertility is of clinical importance as it can have important consequences on the reproductive and general health of the patient. Aurora kinases are serine/threonine kinases that play a vital role in regulating the cell cycle, particularly in ensuring the proper formation of a bipolar spindle and accurate segregation of chromosomes during mitotic cell division. The aurora kinase C (*AURKC*) gene is mainly expressed in the testis. It contributes to chromosomal segregation and cytokinesis and thus could be considered a good candidate gene for male infertility. This study aimed to identify high-risk nonsynonymous single nucleotide polymorphisms (nsSNPs) related to male infertility phenotype in the AURKC gene and predict their pathogenic effect on protein function and stability by applying an in silico approach.

Methods and Materials: The nsSNP data for the Human *AURKC* gene were retrieved from the NCBI dbSNP database (Build 156). The nsSNPs were analyzed using different bioinformatics tools such as SIFT, PolyPhen-2, PROVEAN, CADD, VEST-3, PhD-SNPg, and MutPred2. The INPS-3D server was used to predict the impact of identified pathogenic nsSNPs on the stability of the AURKC protein. The amino acid conservation analysis was performed using the Clustal Omega. The protein sequences were extracted from the UniProt database in FASTA format.

Results: In the first step, 189 nsSNPs were analyzed using SIFT, PolyPhen-2, and PROVEAN tools, and 70 nsSNPs were identified as damaging. These deleterious nsSNPs were further analyzed by CADD, VEST-3, PhD-SNPg, and MutPred2 tools, of which 22 nsSNPs were predicted to be pathogenic by all the tools. Analysis of these pathogenic nsSNPs using INPS-3D server, revealed that A70G, Y156D, Y156H, I167N, C200Y, L228P, C229Y, Y230C and W292C reduce the stability of the protein. Furthermore, amino acid sequence conservation analysis using Clustal Omega indicated that all these nsSNPs affected highly conserved amino acid positions of the AURKC protein. As a result, these nine nsSNPs were considered high-risk nsSNPs related to male infertility phenotype.

Conclusion and Discussion: Our in silico approach identified nine nsSNPs associated with an increased risk for male infertility. Thus, we propose screening for these nsSNPs in infertile men. The findings of this study could be used in clinics and would be helpful for prognosis and diagnosing male infertility in the early years of life.

Keywords: Aurora kinase C, Male infertility, Single nucleotide polymorphisms

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