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P-113 Association of Novel Mutations of TSPY1 Gene With Spermatogenic Failure Among Men

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Study question: Are the novel mutations of TSPY1 gene associated with idiopathic male infertility in men?

Summary answer: Sporadic TSPY1 gene mutation is one of the major causes of idiopathic male infertility among men.

What is known already: As per the published research, there are several studies including AZF micro-deletion, sex chromosome copy number variation but surprisingly studies on Y chromosome genes are not that much available. Due to the genetic cross-talks of different regulatory mechanisms involved in the spermatogenesis process, male infertility still remains idiopathic. Contradictory outcome of the analyses intrigues the association of the variations of TSPY1 gene with male infertility. Previous analyses did not reveal implication of TSPY1 gene as etiologic factor of male infertility.

Study design, size, duration: This was a population-based case-control study that includes 184 cases of spermatogenic failure and 197 age-matched fertile men as controls and the study was conducted between March, 2018 and February, 2021 to infer whether the genetic mutations are significantly associated with spermatogenic failure.

Participants/materials, setting, methods: The samples were collected from the Institute of Reproductive Medicine (IRM) and Genome-the fertility centre. All the selected individuals agreed to participate in the study and provided blood samples. We isolated DNA from the blood samples, designed specific primers and went for PCR. We performed Sanger's dideoxy sequencing of TSPY1 gene reading frame followed by in silico analyses of detected variations to interpret their intuitive effects on transcript and protein level of TSPY1 gene.

Main results and the role of chance: We found one novel deletion namely MN734578 (NC_000024.10:g.9468830del) and one novel insertion MN719944 (NC_000024.10:g.9468815_9468816insA). Both these mutations exhibited strong association with male infertility. MN734578 showed compelling confederacy with male infertility increasing the risk factor against the odd 19.023 (P value 0.0027). Here the mutation was found in 8 out of 184 case individuals. MN719944 was found to be extremely correlated with male infertility increasing the risk factor by 14.547 folds (P value 0.0117). This mutation is found in 6 out of 184 case individuals. Both the mutations were not not found in the control individuals. In silico analyses using different software SIFT,

PROVEAN, REGULATIONSPOTTER, HSF and SpliceAid suggest prospective disruption in splice sites and alteration in different isoforms of TSPY1 transcripts and amino acid sequence in TSPY1 protein. We calculated Odds ratios with respective 95% confidence interval (CI) by performing Fisher's exact test. After Bonferroni's correction, a two-tailed P-value of less than 0.02 was considered statistically significant.

Limitations, reasons for caution: The origin of the novel mutations is unknown and the outcome does not provide mechanistic details how do de novo mutations imperil the process of spermatogenesis.

Wider implications of the findings: The study provides evidence in favour of implication of TSPY1 gene in male fertility. The outcome sheds light to get insight into the issue of unexplained male infertility in Bengali will help to manage fertility problem in men.

Trial registration number: Not applicable