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Role of Toll Like Receptor-2 in Female Genital Tuberculosis Disease Infection and Its Severity

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Abstract : Background: FGTB is now a major global health problem mostly in developing countries including India. In humans, Mycobacterium Tuberculosis (M.tb) is a causating agent of infection. High index of suspicion is required for early diagnosis due to asymptomatic presentation of FGTB disease. In macrophages Toll Like Receptor-2 (TLR-2) is one which mediated host's immune response to M.tb. The expression of TLR-2 on macrophages is important to determine the fate of innate immune responses to M.tb. TLR-2 have two work. First its high expression on macrophages worsen the outer of infection and another side, it maintains M.tb to its dormant stage avoids activation of M.tb from latent phase. Single Nucleotide Polymorphism (SNP) of TLR-2 gene plays an important role in susceptibility to TB among different populations and subsequently, in the development of infertility. Methodology: This Case-Control study was done in the Department of Obs and Gynae and Department of Microbiology at King George's Medical University, U.P, Lucknow, India. Total 300 subjects (150 Cases and 150 Controls) were enrolled in the study. All subjects were enrolled only after fulfilling the given inclusion and exclusion criteria. Inclusion criteria: Age 20-35 years, menstrual-irregularities, positive on Acid-Fast Bacilli (AFB), TB-PCR, (LJ/MGIT) culture in Endometrial Aspiration (EA). Exclusion criteria: Koch's active, on ATT, PCOS, and Endometriosis fibroid women, positive on Gonococal and Chlamydia. Blood samples were collected in EDTA tubes from cases and healthy control women (HCW) and genomic DNA extraction was carried out by salting-out method. Genotyping of TLR2 genetic variants (Arg753Gln and Arg677Trp) were performed by using single amplification refractory mutation system (ARMS) PCR technique. PCR products were analyzed by electrophoresis on 1.2% agarose gel and visualized by gel-doc. Statistical analysis of the data was performed using the SPSS 16.3 software and computing odds ratio (OR) with 95% CI. Linkage Disequiliribium (LD) analysis was done by SNP stats online software. Results: In TLR-2 (Arg753Gln) polymorphism significant risk of FGTB observed with GG homozygous mutant genotype (OR=13, CI=0.71-237.7, p=0.05), AG heterozygous mutant genotype (OR=13.7, CI=0.76-248.06, p=0.03) however, G allele (OR=1.09, CI=0.78-1.52, p=0.67) individually was not associated with FGTB. In TLR-2 (Arg677Trp) polymorphism a significant risk of FGTB observed with TT homozygous mutant genotype (OR= 0.020, CI=0.001-0.341, $p < 0.001$), CT heterozygous mutant genotype (OR=0.53, CI=0.33-0.86, p=0.014) and T allele (OR=0.463, CI=0.32-0.66, $p < 0.001$). TT mutant genotype was only found in FGTB cases and frequency of CT heterozygous more in control group as compared to FGTB group. So, CT genotype worked as protective mutation for FGTB susceptibility group. In haplotype analysis of TLR-2 genetic variants, four possible combinations, i.e. (G-T, A-C, G-C, and A-T) were obtained. The frequency of haplotype A-C was significantly higher in FGTB cases (0.32). Control group did not show A-C haplotype and only found in FGTB cases. Conclusion: In conclusion, study showed a significant association with both genetic variants of TLR-2 of FGTB disease. Moreover, the presence of specific associated genotype/alleles suggest the possibility of disease severity and clinical approach aimed to prevent extensive damage by disease and also helpful for early detection of disease.

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