Impact of promoter polymorphisms of apoptotic signaling regulatory genes FAS/FASL on chronic myeloid leukemia susceptibility risk

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Abstract

Chronic myeloid leukemia (CML) is a stem cell disorder in which Philadelphia (Ph) chromosome is implicated in the etiopathogenesis. Ph chromosome translocation results in the formation of BCR-ABL oncogene which is known to deregulate different downstream pathways which ultimately lead to cell proliferation, defective DNA repair, and inhibition of apoptosis. But evidence show that the Ph chromosome alone is insufficient for development of CML. Host genetic susceptibility factors which favours CML development are not clear. Fas cell surface death receptor (FAS) is a member of tumor necrosis factor superfamily which interacts with its ligand, FASL to initiate apoptosis. Promoter polymorphisms in FAS/FASL genes are known to influence the apoptotic signaling and influence carcinogenesis. So this study was undertaken in a total of 191 subjects (93 CML patients and 98 normal control) to investigate the frequencies and impact of $FAS-670 A>G$ and $FASL-844 T>C$ polymorphism on CML susceptibility risk. After getting written consent, blood samples of study subjects were collected, DNA extraction done from blood samples and genotyping was performed using PCR-RFLP technique. The genotypes were categorized into homozygous wild type, heterozygous and homozygous variant. The association of the genotypes with CML susceptibility risk was assessed by means of logistic regression analysis and deriving odds Ratio with 95% CI. Homozygous wild genotype was used as reference. Few representative genotypes were validated using DNA sequencing. Data was analyzed using SPSS Version 22. On evaluating the impact, the study revealed a significant association of $FASL-844 T>C$ polymorphisms with CML susceptibility risk. Both variant C allele (OR 1.756, CI 1.163,2.652, $p=0.007$) and variant genotype CC of $FASL-844$ (OR 2.261, CI 1.013,5.047, $p=0.047$) carried significantly higher risk for CML development. The heterozygous genotype TC significantly conferred lower risk for CML susceptibility (OR 0.379, CI 0.176,0.816, $p=0.013$) For $FAS-670 A>G$ polymorphism, both heterozygous genotype AG and variant genotype GG showed higher values (OR 1.642 CI, 0.719-3.750 and OR 1.133, CI 0.464-2.768, respectively) but were statistically insignificant ($p= 0.239$ and $p= 0.784$ respectively). Our results highlight the impact of $FASL-844 T>C$ polymorphism on CML susceptibility risk. This novel finding might be helpful in early identification of individuals who are at higher risk for development of CML.

Keywords: Chronic myeloid leukemia; susceptibility risk; FAS/FASL; promoter polymorphism

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