Title:	Investigating the pathogenic SNPs in BLM helicase and their biological consequences by computational approach
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Abstract:	The BLM helicase protein plays a vital role in DNA replication and the maintenance of genomic integrity. Variation in the BLM helicase gene resulted in defects in the DNA repair mechanism and was reported to be associated with Bloom syndrome (BS) and cancer. Despite extensive investigation of helicase proteins in humans, no attempt has previously been made to comprehensively analyse the single nucleotide polymorphism (SNPs) of the BLM gene. In this study, a comprehensive analysis of SNPs on the BLM gene was performed to identify, characterize and validate the pathogenic SNPs using computational approaches. We obtained SNP data from the dbSNP database version 150 and mapped these data to the genomic coordinates of the “NM_000057.3” transcript expressing BLM helicase (P54132). There were 607 SNPs mapped to missense, 29 SNPs mapped to nonsense, and 19 SNPs mapped to 3′-UTR regions. Initially, we used many consensus tools of SIFT, PROVEAN, Condel, and PolyPhen-2, which together increased the accuracy of prediction and identified 18 highly pathogenic non-synonymous SNPs (nsSNPs) out of 607 SNPs. Subsequently, these 18 high-confidence pathogenic nsSNPs were analysed for BLM protein stability, structure–function relationships and disease associations using various bioinformatics tools. These 18 mutants of the BLM protein along with the native protein were further investigated using molecular dynamics simulations to examine the structural consequences of the mutations, which might reveal their malfunction and contribution to disease. In addition, 28 SNPs were predicted as “stop gained” nonsense SNPs and one SNP was predicted as “start lost”. Two SNPs in the 3′UTR were found to abolish miRNA binding and thus may enhance the expression of BLM. Interestingly, we found that BLM mRNA overexpression is associated with different types of cancers. Further investigation showed that the dysregulation of BLM is associated with poor overall survival (OS) for lung and gastric cancer patients and hence led to the conclusion that BLM has the potential to be used as an important prognostic marker for the detection of lung and gastric cancer
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