

COMPUTATIONAL FUNCTIONAL PRIORITIZATION OF XRCC1 MISSENSE VARIANTS ASSOCIATED WITH LEUKEMIA SUSCEPTIBILITY

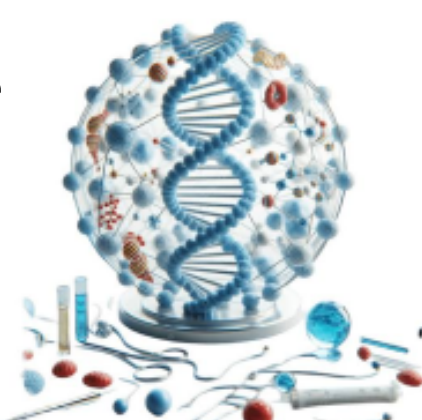
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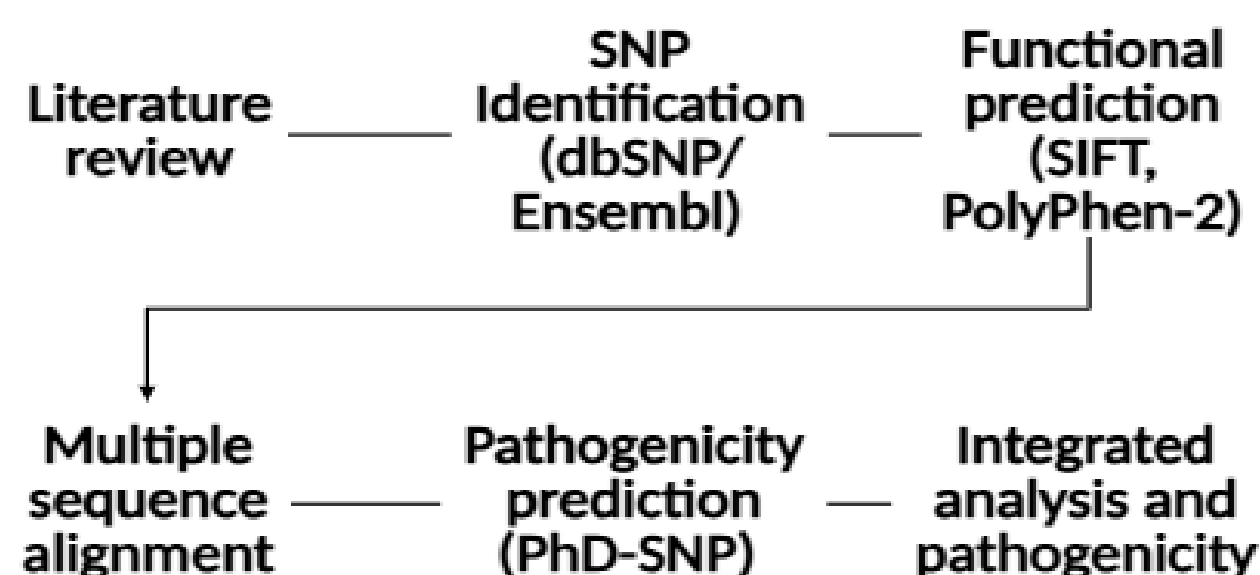


INTRODUCTION

- Leukemia is a set of blood-based cancers that are caused by genetic mutations
- XRCC1* plays an important role in the base excision repair (BER) pathway
- Missense variants in *XRCC1* may have a significant effect on *XRCC1* protein function and DNA repair
- Computational analysis can be used to prioritize variants that may have functional effects



METHODOLOGY



RESULTS

Variant	c-DNA	Amino Acid	Exon
rs1799782	580C>T	Arg194Trp	6
r25489	839G>A	Arg280His	9
rs25487	1196A>G	Arg399Gln	10

Table 1: Selected *XRCC1* SNPs and Ensembl Variant Verification

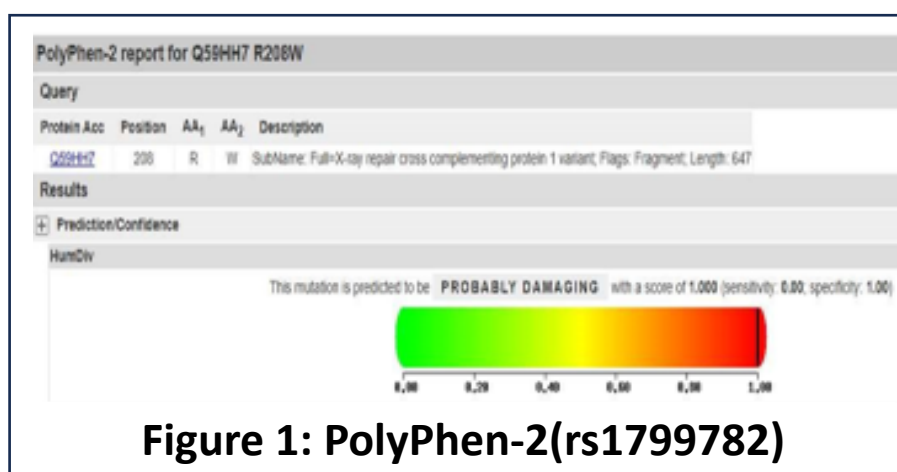


Figure 1: PolyPhen-2(rs1799782)

Variant	SIFT (Score/Prediction)	PolyPhen-2 (Score/Prediction)	PhD-SNP (Score/Prediction)
rs1799782	0.00 (Deleterious)	1.000 (Probably damaging)	Neutral
r25489	0.00 (Deleterious)	0.002 (Benign)	Neutral
rs25487	1.00 (Tolerated)	0.000 (Benign)	Neutral

Table 2: Predicted functional effects of selected *XRCC1* missense SNPs using SIFT, PolyPhen-2, and PhD-SNP

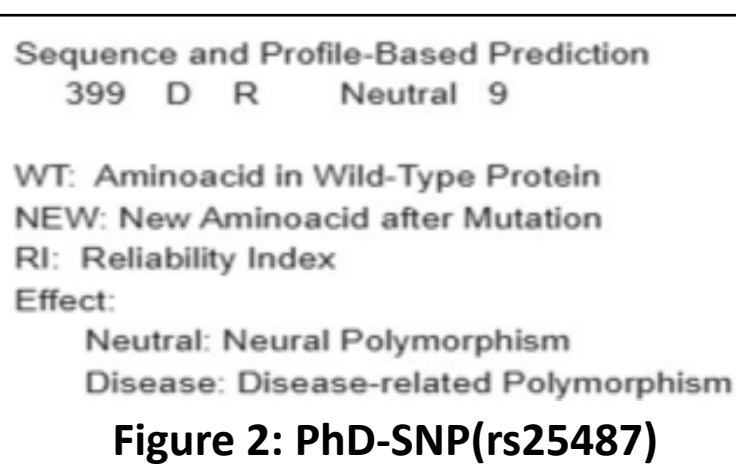


Figure 2: PhD-SNP(rs25487)

Substitution at pos 280 from R to H is predicted to **AFFECT PROTEIN FUNCTION** with a score of 0.00. Median sequence conservation: 4.32 Sequences represented at this position:4

Figure 3: SIFT(rs25489)

rs1799782	rs25487	rs25489
3ALFFSRINKTSPVTASDPAC	DCHRMRRRLPSQRYLMAGPC	PKLPAPTITPATAP--VPARAQ
3ALFFSRINKAASASASDPA	DCYRMRRRLPSRRLMAGLC	PKLPVPSRTPAATP--ASTPAQ
3ALFFSRINKTSSASTSDPAC	DCHHMRRRLPSRRLMAGLC	PKLSVPSRTPAAP--ASTPAQ
3ALFFSRNNKTSTATASDPA	DCHRMRRRLPSRRLMAGPG	PKLPAPTITPATAP--VPAAAR
3ALFFSRINKTSPVTASDPAC	DCHRMRRRLPSRRLMAGPG	PKLPAPTITPATAP--VPARAQ
3ALFFSRINKTSPATVSDPAC	DCHRMRRRLPSRRLMAGPG	PKLPAPTITPATAP--APVPGQ
3ALFFSRINKTSPATASDPAC	DCHRMRRRLPSRRLMAGPG	PKLPVPTHTTATAPAPVPAPAC
3ALFFSRINKTSPVTASDPAC	DCHRMRRRLPSRRLMAGTG	PKLPAPTITPATAP--VPAPAQ
3ALFFSRVKKTSALASDLAC	DCHRMRRRLPSRRLMAGPD	PKLPAPTITPATAP--VPAPAQ
PGS-----EGGGAG	DCHRMRRRLPSRRLMAGPS	ASTVPAPSRTPAVAP--VPAAAC
3ALFFSRINKTSPVTASDPAG	DCHRMRRRLPSRRLMAGPG	PKLPAPTITPAAPV--VPAPAC
3ALFFSRINKTTPAASDPAGE	DCHRMRRRLPSRRLMAGPDS	PKLPAAPTITPATAP--LPAPAR

Figure 4 **Figure 5** **Figure 6**
Multiple sequence alignment showing conservation of the three selected *XRCC1* variants.

DISCUSSION

- Associations of *XRCC1* variants: rs1799782, rs25489 and rs25487 with susceptibility to leukemia have been previously reported with variation across populations
- In the present analysis rs1799782 (Arg194Trp) had the highest predicted functional impact
- Variant rs25489 (Arg280His) also showed potential functional relevance, while rs25487 (Arg399Gln) showed a relatively neutral prediction profile

CONCLUSION

- The results indicate functional heterogeneity of the three *XRCC1* missense variants
- These variants might have different effects on *XRCC1*-mediated DNA repair and leukemia susceptibility
- Experimental studies are needed to further confirm their biological relevance

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