

Mutation Analysis Of the BRCA1 Gene

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DOI: <https://doi.org/10.63363/aijfr.2026.v07i05.8483>

Abstract

This study investigates the functional impact of specific missense mutations in the Breast Cancer Type 1 (BRCA1) protein using computational prediction tools SIFT and PolyPhen-2. BRCA1 is a critical tumor suppressor involved in DNA repair and cell cycle regulation. By analyzing mutations in highly conserved domains (RING finger and the BRCT) compared to linker regions, we demonstrate the predictive accuracy of evolutionary conservation and structural bioinformatics in identifying pathogenic variants. Results indicate a high consensus between SIFT and PolyPhen-2 for known pathogenic variants, such as C61G and M1775R, while highlighting the benign nature of common polymorphisms like K1183R.

1. Introduction

The BRCA1 gene, located on Chromosome 17q21, encodes a large nuclear protein that plays a pivotal role in maintaining genomic stability. It functions primarily through the repair of DNA double-strand breaks via homologous recombination and the regulation of the G2/M cell cycle checkpoint. Pathogenic mutations in BRCA1 significantly increase the lifetime risk of hereditary breast and ovarian cancers.

To predict whether a single amino acid substitution (missense mutation) is likely to disrupt protein function, researchers utilize silico tools. SIFT predicts the impact of an amino acid substitution based on the degree of conservation of amino acid residues in sequence alignments derived from closely related proteins. PolyPhen-2 predicts the possible impact of amino acid substitutions on the stability and function of human proteins using structural and comparative evolutionary considerations.

2. Methodology

2.1 Sequence Acquisition

The reference amino acid sequence for the human BRCA 1 protein was obtained. The protein consists of 1863 amino acids and contains key functional domains, including the N-terminal RING finger domain (residues 1-109) and two C-terminal BRCT domains (residues 1646-1859).

2.2 Selection of Mutations

Four representative mutations were selected for the analysis based on their clinical significance in databases such as Clinvar and existing literature:

- C61G (Cysteine to Glycine): Located in the RING finger domain, essential for E3 ubiquitin ligase activity

- M1775R (Methionine to Arginine): Located in the BRCT domain, critical for phosphoprotein binding
- S1613G (Serine to Glycine): A variant often discussed in the contest of phenotypic variability
- K1183R (Lysine to Arginine): A common polymorphism located in a non-conserved linker region

2.3 Prediction tools

Variants were analyzed using SIFT (score $S \leq 0.05$ is deleterious) and PolyPhen-2 (score near 1.0 is damaging)

Results

The computational scores for the selected BRCA1 variants are summarized in Table 1 below

Mutation	Domain Location	SIFT Score	PolyPhen-2 Score	Final Prediction
C61G	RING Finger	0.00 (Deleterious)	1.000 (Damaging)	Pathogenic
M1775R	BRCT Domain	0.00 (Deleterious)	0.999(Damaging)	Pathogenic
S1613G	BRCT Region	0.01 (Deleterious)	0.852 (Damaging)	Likely Pathogenic
K1183R	Linker Region	0.18 (Tolerated)	0.012 (Benign)	Benign

Discussion

The analysis reveals a strong correlation between the location of a mutation and its predicted pathogenicity. The C61G mutation disrupts the Zinc-binding site within the RING finger domain, which is vital for the interaction with BARD1 and subsequent ubiquitin ligase activity (Sweet et al. 2009). The high PolyPhen-2 score (1.000) reflects the severe structural disruption caused by replacing a small, polar-neutral Cysteine with a Glycine in a sensitive binding pocket.

Similarly, the M1775R mutation in the BRCT domain is a well-documented pathogenic variant that prevents the recruitment of BRCA1 to sites of DNA damage (Nelson & Holt, 2010). The K1183R mutation, by contrast, involves a substitution between two chemically similar amino acids (Lysine and Arginine) in a region of the protein that lacks high evolutionary conservation, leading to “Benign” and “Tolerated” classifications across both tools.

Conclusion

In silico tools like SIFT and PolyPhen-2 are effective first-line resources for prioritizing genetic variants in BRCA1. Our findings confirm that mutations in highly conserved, structurally rigid domains are significantly more likely to be deleterious than those in disordered linker regions. Future work should combine these computational predictions with functional assays and family segregation data for definitive clinical classification.

References

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