







Impact of the existence of isoforms on the assessment of the evolutionary conservation of amino acid residues in the RAD51C protein: Implications for the classification of genetic variants regarding pathogenicity

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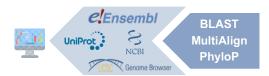
INTRODUCTION

The RAD51C protein participates in DNA repair by homologous recombination. Mutations in RAD51C have been associated with a higher risk of breast and/or ovarian cancer. The depth of evolutionary conservation of the mutated amino acid residue is an important criterion in classifying genetic variants for pathogenicity. Still, its estimation could be affected by the existence of isoforms in humans and other species.

OBJECTIVES

To evaluate the impact of RAD51C protein isoforms in humans and other species on the classification process of genetic variants regarding pathogenicity.

METHODOLOGY



RESULTS AND DISCUSSION

In humans, seven isoforms of the RAD51C protein have been identified, and the canonical one has 376 residues.

Figure 1 - Human RAD15C protein isoforms



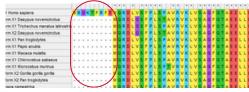
The fraction of highly conserved residues among the 376 of the canonical isoform varied according to the software used: ConSurf (60), PhyloP/UCSC Genome Browser (176), and Clustal/MEGA X (72).

Figure 2 - Evolutionary conservation by residue of RAD51C



Analysis with a cluster of 32 sequences showed that from residue 10 on of the canonical human isoform, all primate sequences identified in this cluster were highly conserved.

Figure 3 - Multiple alignment of human RAD51C protein



CONCLUSION

The existence of isoforms hinders the analysis of evolutionary conservation and the estimation of the depth of evolutionary conservation of several residues, which affects the classification of genetic variants in RAD51C regarding pathogenicity.

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