MODELING AND MOLECULAR DYNAMICS OF GENETIC VARIANTS OF THE HUMAN NEK1 PROTEIN IN AMYOTROPHIC LATERAL SCLEROSIS

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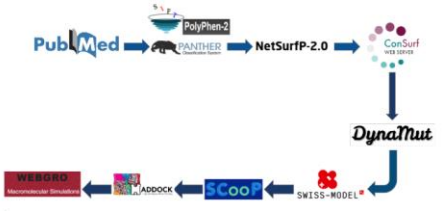
INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons. NEK1 stands out among ALS-associated genes due to its roles in cell cycle control, cilia assembly, and apoptosis. To evaluate, through *in silico* analysis, the effects of NEK1 variants on the structure and function of its encoded protein.

METHODOLOGY



RESULTS

Variant ID	PolyPhen-2	SIFT	PANTHER
rs756261702	Probably damage	Deleterious	Probably damage
rs1309738215	Probably damage	Deleterious	Probably damage
rs772747361	Probably damage	Deleterious	Probably damage
rs200161705	Probably damage	Deleterious	Probably damage

Table 1. Functional impact prediction, all platforms indicated that the variants have deleterious effects on the protein.

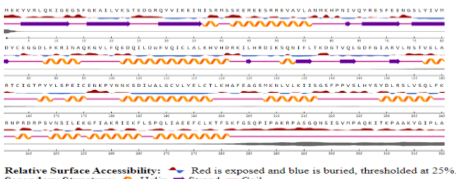


Figure 1. Structural impact prediction. NetSurP indicated that the K214R, R232 and R261H variants were classified as exposed and highly conserved, and the C113R variant was classified as buried.

NetSurP and Consurf classified the variants K214R, R232H, and R261H as exposed and highly conserved, suggesting critical functional roles. Adittionally, model quality analysis descreibed that structures containing the kinase domain had better stereochemical quality. SCooP results indicated that the variants rendered the protein thermolabile, affecting its functional temperature range. On the hand, molecular docking revealed reduced ATP binding affinity in the C113R and K214R variants, while molecular dynamics simulations showed that all isoforms exhibited decreased stability and flexibility.

SUPPORT

UFG CAPES AGORA

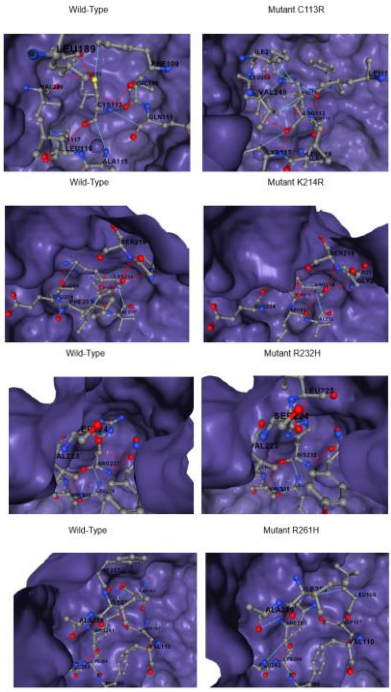


Figure 2. Interactions predicted by DynaMut. According to the DynaMut analysis, all variants caused destabilizing effects on the proteins. In addition, the exchange of amino acids altered the dynamics of the interactions, modifying the pattern of interactions between the wild-type and mutant forms of the protein. Hydrogen bonds are represented by red lines and Van der Waals interactions are represented by blue lines.

DISCUSSION

The consistent classification of NEK1 variants as deleterious by multiple predictive tools underscores their potential pathogenic role in ALS. The identification of K214R, R232H, and R261H as exposed and highly conserved residues by NetSurP and ConSurf highlights their likely importance in maintaining NEK1, structural and functional integrity. Structural analyses further support this, with DynaMut revealing destabilizing effects and altered intramolecular interactions, which may impair protein folding or enzymatic activity. The reduced thermostability observed suggests that these variants compromise the protein's resilience under physiological conditions. Additionally, molecular docking and dynamics simulations demonstrated impaired ATP binding and decreased structural stability and flexibility, respectively.

CONCLUSION

Collectively, these findings suggest that NEK1 variants may disrupt proteostasis, a key factor in ALS pathogenesis and other neurodegenerative disorders.

REFERENCES

References

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