

Mechanisms of Loss of Functions of Human Angiogenin Variants Implicated in Amyotrophic Lateral Sclerosis

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Abstract

Mutations in the coding region of angiogenin (*ANG*) gene have been found in patients suffering from Amyotrophic Lateral Sclerosis (ALS). Neurodegeneration results from the loss of angiogenic ability of *ANG* (protein coded by *ANG*). In this work, we performed extensive molecular dynamics (MD) simulations of wild-type *ANG* and disease associated *ANG* variants to elucidate the mechanism behind the loss of ribonucleolytic activity and nuclear translocation activity, functions needed for angiogenesis.

MD simulations were carried out to study the structural and dynamic differences in the catalytic site and nuclear localization signal residues between WT-*ANG* (Wild-type *ANG*) and six mutants. Variants K17I, S28N, P112L and V113I have confirmed association with ALS, while T195C and A238G single nucleotide polymorphisms (SNPs) encoding L35P and K60E mutants respectively, have not been associated with ALS. Our results show that loss of ribonucleolytic activity in K17I is caused by conformational switching of the catalytic residue His114 by 99°. The loss of nuclear translocation activity of S28N and P112L is caused by changes in the folding of the residues ³¹RRR³³ that result in the reduction in solvent accessible surface area (SASA). Consequently, we predict that V113I will exhibit loss of angiogenic properties by loss of nuclear translocation activity and L35P by loss of both ribonucleolytic activity and nuclear translocation activity. No functional loss was inferred for K60E. The MD simulation results were supported by hydrogen bond interaction analyses and molecular docking studies.

Conformational switching of catalytic residue His114 seems to be the mechanism causing loss of ribonucleolytic activity and reduction in SASA of nuclear localization signal residues ³¹RRR³³ results in loss of nuclear translocation activity in *ANG* mutants. Therefore, we predict that L35P mutant, would exhibit loss of angiogenic functions, and hence would correlate with ALS while K60E would not show any loss.