Structural Impact of the Mutation in RRM: Insights into RNA-Binding Alterations Linked to Autism Spectrum Disorder

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Abstract:

Background: Autism Spectrum Disorder (ASD) is a heritable neurodevelopmental condition in which mutations in RNA-binding proteins (RBPs) have emerged as functionally significant contributors. HTATSF1, a nuclear RBP involved in transcriptional elongation and pre-mRNA splicing, harbours a missense variant F298L identified in an ASD patient (Al-Mubarak et al., 2017). This substitution replaces a conserved aromatic phenylalanine within the RNA Recognition Motif 1 (RRM1) domain with an aliphatic leucine, potentially disrupting RNA binding.

Objectives: This study characterises the evolutionary conservation of F298, models the structural consequences of the F298L substitution, and evaluates its impact on protein–RNA binding affinity.

Methods: Multiple sequence alignment of 100 curated eukaryotic RRM proteins was performed using MAFFT v7 (L-INS-i). Structures were retrieved from the PDB (HTATSF1: 6Y5Q; FUS: 6SNJ; TDP-43: 4Y0F; U1A: 1DRZ), prepared in UCSF Chimera, and the F298L variant was modelled using AlphaFold and analysed in PyMOL. Protein–RNA docking was conducted using HADDOCK 2.4 and HDOCK.

Results: F298 was strictly conserved across all proteins analysed. The F298L substitution produced local conformational distortion within RRM1, disrupting π–π aromatic stacking interactions critical for RNA recognition. HTATSF1 F298L exhibited the most detrimental docking profile among the four proteins, consistent with findings from equivalent mutations in FUS, TDP-43, and U1A.

Conclusion: The F298L mutation structurally distorts the HTATSF1 RRM1 domain and significantly reduces RNA-binding affinity, implicating RNA processing dysregulation as a potential mechanism in ASD pathogenesis. Further in vitro and in vivo studies are warranted.

Keywords:

HTATSF1, ASD, F298L, RRM domain, RNA-binding protein, HADDOCK, MAFFT.