

Somatic N-terminal TARDBP variants identified in the brain of FTD-TDP-C patients disrupt physiological function in zebrafish

Leslie Sanderson, Herma van der Linde, Merel Mol, Shamiram Melhem, Lot van Ulft, John van Swieten, Tjakko van Ham, Jeroen van Rooij

Introduction: Pathogenic germline variants in *TARDBP* cause amyotrophic lateral sclerosis and frontotemporal dementia with TDP pathology. Recently, we identified somatic *TARDBP* variants in the brains of two semantic dementia patients with FTD-TDP type C pathology. These two variants (L41F and R42H) were identified in the N-terminal domain. To date, the vast majority of functional studies have focused on the C-terminus, which is where the known pathogenic germline variants are located. **Methods:** To assess the pathogenic potential of the N-terminal variants, we compared their impact *in vivo* using zebrafish against known pathogenic germline variants (P112H, K263E, and I383V). **Results:** In line with *in silico* predictions, we show that the L41F and K263E alleles are less well tolerated in *in vivo* toxicity assays, displaying a toxic gain of function when ubiquitously expressed. Similarly, the L41F allele, followed by K263E and P112H, showed substantial loss of function in a full knockout system designed to assess their rescue capacity. Interestingly, while the R42H and I383V alleles did not demonstrate clear toxicity or loss of function in these assays, we did detect a possible immunogenic effect. Additionally, a novel zebrafish line carrying a G37del variant was also characterized, showing significant gross morphological abnormalities. **Discussion:** Together, these data provide evidence of the pathogenicity of N-terminal variants, including L41F and R42H, and suggest that some germline variants in this domain may not be compatible with life, contributing to their low frequency of germline detection and further reinforcing the importance of considering somatic contributions in TDP43-related disease.

Conflicts of interest

Nothing to disclose.