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**Title: BIALLELIC LOSS-OF-FUNCTION MUTATIONS IN THUMPD1 AFFECT TRNA ACETYLATION AND CAUSE A SYNDROMIC NEURODEVELOPMENTAL DISORDER**

**Abstract:**

Chemical tRNA modifications play various roles in tRNA biology, including stability, folding, and recognition, as well as the rate and fidelity of translation, and therefore contribute to essential cellular processes such as growth and development. Mutations in genes that are known to regulate tRNA modifications lead to a wide array of phenotypes and diseases including numerous cognitive and neurodevelopmental disorders, highlighting the critical role of tRNA modification in human disease. One such gene, THUMPD1, an ortholog of yeast TAN1 previously suggested to be required for tRNA N4-acetylcytidine modification (ac4C), recently was proposed as a candidate gene for autosomal-recessive intellectual disability. Study of 13 individuals from 8 families who harbor loss-of-function variants in THUMPD1 showed common phenotypic abnormalities included global developmental delay, speech delay, moderate to severe intellectual deficiency, behavioral abnormalities such as angry outbursts, facial dysmorphism, and ophthalmological abnormalities. We demonstrated that the biallelic variants identified caused a substantial decrease of THUMPD1 protein expression (and therefore its function) and that this defect resulted in a loss of ac4C modification in small RNAs, and of individually purified tRNA-Ser-CGA. We further corroborated this effect by showing a loss of tRNA acetylation in two independent CRISPR-Cas9-generated THUMPD1 KO cell lines. In addition, we also showed that the resultant amino acid substitution that occurs in a missense THUMPD1 allele identified in an individual with compound heterozygous variants resulted in a marked decrease in THUMPD1 protein stability and its RNA-binding capacity. Taken together, our data suggest that the lack of tRNA acetylation due to the loss of THUMPD1 function results in a syndromic form of developmental alterations and intellectual disability.