Loss-of-function variants of SETD5 cause intellectual disability and the core phenotype of microdeletion 3p25.3 syndrome.

Intellectual disability (ID) has an estimated prevalence of 2-3%. Due to its extreme heterogeneity, the genetic basis of ID remains elusive in many cases. Recently, whole exome sequencing (WES) studies revealed that a large proportion of sporadic cases are caused by de novo gene variants. To identify further genes involved in ID, we performed WES in 250 patients with unexplained ID and their unaffected parents and included exomes of 51 previously sequenced child-parents trios in the analysis. Exome analysis revealed de novo intragenic variants in SET domain-containing 5 (SETD5) in two patients. One patient carried a nonsense variant, and the other an 81 bp deletion located across a splice-donor site. Chromosomal microarray diagnostics further identified four de novo non-recurrent microdeletions encompassing SETD5. CRISPR/Cas9 mutation modelling of the two intragenic variants demonstrated nonsense-mediated...
decay of the resulting transcripts, pointing to a loss-of-function (LoF) and haploinsufficiency as the common disease-causing mechanism of intragenic SETD5 sequence variants and SETD5-containing microdeletions. In silico domain prediction of SETD5, a predicted SET domain-containing histone methyltransferase (HMT), substantiated the presence of a SET domain and identified a novel putative PHD domain, strengthening a functional link to well-known histone-modifying ID genes. All six patients presented with ID and certain facial dysmorphisms, suggesting that SETD5 sequence variants contribute substantially to the microdeletion 3p25.3 phenotype. The present report of two SETD5 LoF variants in 301 patients demonstrates a prevalence of 0.7% and thus SETD5 variants as a relatively frequent cause of ID.