

***SETD5* gene variant associated with mild intellectual disability - a case report**

E. Stur, L.A. Soares and I.D. Louro

Programa de Pós-Graduação em Biotecnologia,
Núcleo de Genética Humana e Molecular, Departamento de Ciências Biológicas,
Universidade Federal do Espírito Santo, Vitória, ES, Brasil

Corresponding author: E. Stur
E-mail: elainestur@gmail.com

Genet. Mol. Res. 16 (2): gmr16029615
Received January 13, 2017
Accepted April 13, 2017
Published May 25, 2017
DOI <http://dx.doi.org/10.4238/gmr16029615>

Copyright © 2017 The Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution ShareAlike (CC BY-SA) 4.0 License.

ABSTRACT. The recent advent of exome sequencing has allowed for the identification of pathogenic gene variants responsible for a variety of diseases that were previously clinically diagnosed, with no underlying molecular etiology. Among these conditions, intellectual disability is a prevalent heterogeneous condition, presenting itself in a large spectrum of intensity, in some cases associated with congenital malformations, behavioral and various other intellectual development alterations. Here we report on a 36-year-old male patient, with a mild intellectual disability that remained undiagnosed at the molecular level for all his life. Using Nextera Exome Sequencing, a Chr3:9.517.294 A>AC (c.3848_3849insC) *SETD5* gene insertion was found. This rare variant was classified as likely pathogenic due to its frameshift nature in the gene, in which loss-of-function mutations have been previously reported to cause intellectual disability, as well as a 3p25.3 microdeletion phenotype. It is possible that this variant shows partial activity, due to its gene localization, which would explain the patient's mild phenotype when compared with other reports.

Key words: *SETD5* protein; Human intellectual disability; DNA sequencing

INTRODUCTION

Intellectual disability (ID) is a group of diseases with cognitive developmental delay. ID is most commonly found during childhood, with prevalence ranging from 1-3% (Hamdan et al., 2009a,b; Rauch et al., 2012).

ID includes phenotypes such as congenital malformation, hypotonia, feeding difficulties, speech and motor deficits, growth retardation, cardiovascular and renal defects, epilepsy, hearing impairment, craniofacial features with brachycephaly and prominent high forehead, and long, thin and tubular nose. Skeletal features include thoracic scoliosis, kyphosis, and lordosis. Furthermore, behavioral issues as obsessive-compulsive disorder and autism are commonly found (Gunnarsson and Foyn Bruun, 2010; Cooper et al., 2011; Grozeva et al., 2014).

Recent studies have identified several mutations in autosomal and X-chromosomes supporting the idea that more than 2000 genes participate in the intellectual development, but the complete genetic basis for ID is still unclear, due in large part to its high heterogeneity (Hamdan et al., 2009a; Rauch et al., 2012; Grozeva et al., 2014).

Currently, next-generation sequencing and microarray studies have identified indels that cause loss of function alterations (LoF) and copy number variation (CNV) in individuals with ID, since all cases have some CNVs, most of which are rated as benign (Hamdan et al., 2009b; Gunnarsson and Foyn Bruun, 2010; Cooper et al., 2011; Rauch et al., 2012; Grozeva et al., 2015). *De novo* CNVs are the most common ID etiology, indicating that monoallelic alterations are sufficient to cause disease by LoF resulting in haploinsufficiency (Hamdan et al., 2009a; Kuechler et al., 2015).

Recently, *SETD5* gene mutations were associated with ID. The *SETD5* gene encodes a protein that regulates transcription. Large and small deletions as well nonsense, stop mutations, and frameshift mutations in this gene may result in premature stop codons leading to developmental diseases, as the 3p syndrome and other IDs (Grozeva et al., 2014; Sowalsky et al., 2015).

Here, we report a patient with non-syndromic intellectual disability and a *SETD5* C insertion (Chr3p25: 9.517.294).

MATERIAL AND METHODS

Clinical report

A 36-year-old male patient, with two healthy brothers from nonconsanguineous parents, was clinically diagnosed with mild motor and intellectual disability, myopia, and astigmatism. His physical parameters were normal, weighing 65 kg, 178 cm of height, and a head circumference of 57.5 cm. Brain magnetic resonance and chest echo Doppler showed no morphological alterations. Metabolic tests were all normal. The parents provided a written informed consent for this study.

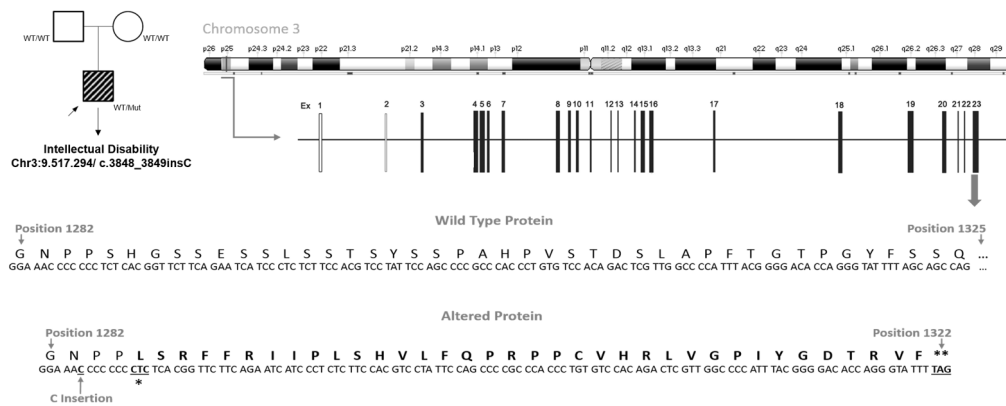
Sequencing

Patient's blood was collected and sent to Mendelics Laboratory (São Paulo, Brazil). Sequencing was performed as Nextera Exome Rapid Capture (77-bp paired-end reads;

coverage: 97.47% at a minimum of 20 reads) on Illumina HiSeq (Illumina, San Diego, CA, USA). The alignment was based on the GRCh37 human genome assembly. The mutation found was confirmed and parents were also analyzed by Sanger's sequencing.

RESULTS

Sequencing revealed the Chr3:9.517.294 A>AC variant (or alternatively, c.3848_3849insC - CCDS46741.1) affecting one copy of the *SETD5* gene (set domain-containing protein 5, OMIM #615743), and causing the substitution of a serine at position 1286 for leucine; This is a frameshift mutation that creates a premature stop codon (p.Ser1286Leu), at position 1322 (Figure 1). This variant was described as probably pathogenic, with a possible loss of function for the *SETD5* gene product. No other variants were reported. Parents tested negative for this particular variant by Sanger's sequencing, suggesting that this was a *de novo* mutation (Figure 2).



DISCUSSION

Although there are several types of intellectual disabilities, they can generally be characterized by specific features such as speech and motor deficits, growth retardation, cardiovascular and renal defects, and behavioral issues such as autism spectrum disorders, obsessive compulsive disorders, and hand flapping behavior (Grozeva et al., 2014; Pinto et al., 2014). These features can vary according to the main underlying genetic cause and genotype-phenotype specific correlations (Riess et al., 2012).

Although rare, patients with IDs may present large deletions (up to 12 Mb), small deletions, substitutions, and insertions (Riess et al., 2012). Our results suggest a new *de novo* *SETD5* gene variant (Chr3:9.517.294/ c.3848_3849insC) as the genetic cause of ID in this patient.

In 2014, Grozeva et al. identified 7 new mutations in the *SETD5* gene in patients with ID, including 4 substitutions, 2 deletions, and 1 duplication. Rauch et al. (2012) described a new one, Kuechler et al. (2015) and Szczafuba et al. (2016) described 2 variants each one, and

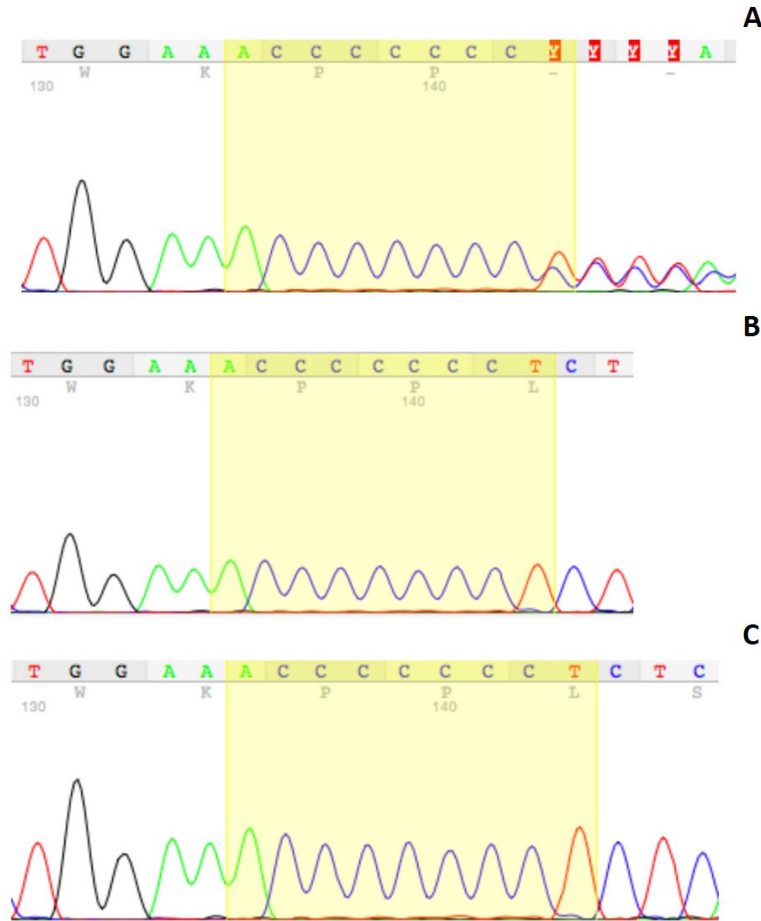


Figure 2. Sanger's sequencing electropherogram of the region verified by Sanger sequencing. **A.** Patient with the variant. **B.** Father without the variant. **C.** Mother without the variant.

Kobayashi et al. (2016) described 1 *de novo* mutation. These data show that mutations are commonly found in ID. The 3p syndrome is rare, but well described and commonly caused by *de novo* mutations (Grozeva et al., 2015).

When compared to other studies, our patient shows a milder phenotype, probably due to large deletions encompassing several genes in more severely affected patients (Gunnarsson and Foyn Bruun, 2010; Peltekova et al., 2012; Kuechler et al., 2015; Kellogg et al., 2013).

The 4329-bp *SETD5* gene encodes a 1442-amino acid protein, which is highly conserved in mammalian species. *SETD5* mRNA is highly expressed in the cerebral cortex, intestine, and the eye, but its exact role is still unclear. Recent studies showed that *SETD5* might function as a transcription regulator because similar domains are frequently found in nuclear proteins that interact with chromatin (Grozeva et al., 2015; Kuechler et al., 2015; Sowalsky et al., 2015).

The fact that the *SETD5* protein is expressed in the eye may explain vision problems reported in this patient. Our patient shows a small insertion, while most patients have large deletions in genes that participate in the mental and physical development (Kuechler et al., 2015).

Moreover, the reported insertion (c.3848_3849insC) happened at the end of the gene in a disordered region and not in known domains (*in silico* prediction) (Kuechler et al., 2015). Although this mutation leads to a premature stop codon, this variant may not cause a complete loss of function protein version due to the mutation location at the end of the protein, which would explain the mild patient's phenotype. Mutations in the C-terminal region could be associated with weaker phenotype due to a possible escape from the *NMD* system (nonsense-mediated mRNA decay), that eliminates mRNAs containing premature translation termination codons (Brojna and Wen, 2009; Szczałuba et al., 2016).

In conclusion, we describe a new probably pathogenic variant, as the putative genetic cause of this patient's motor and cognitive dysfunctions.

ACKNOWLEDGMENTS

We would like to thank the patient and his parents for the help we received in putting this information together.

REFERENCES

- Brojna S and Wen J (2009). Nonsense-mediated mRNA decay (NMD) mechanisms. *Nat. Struct. Mol. Biol.* 16: 107-113. <https://doi.org/10.1038/nsmb.1550>
- Cooper GM, Coe BP, Girirajan S, Rosenfeld JA, et al. (2011). A copy number variation morbidity map of developmental delay. *Nat. Genet.* 43: 838-846. <https://doi.org/10.1038/ng.909>
- Grozeva D, Carss K, Spasic-Boskovic O, Parker MJ, et al.; UK10K Consortium (2014). *De novo* loss-of-function mutations in *SETD5*, encoding a methyltransferase in a 3p25 microdeletion syndrome critical region, cause intellectual disability. *Am. J. Hum. Genet.* 94: 618-624. <https://doi.org/10.1016/j.ajhg.2014.03.006>
- Grozeva D, Carss K, Spasic-Boskovic O, Tejada MI, et al.; Italian X-linked Mental Retardation Project; UK10K Consortium; GOLD Consortium (2015). Targeted next-generation sequencing analysis of 1,000 individuals with intellectual disability. *Hum. Mutat.* 36: 1197-1204. <https://doi.org/10.1002/humu.22901>
- Gunnarsson C and Foyn Bruun C (2010). Molecular characterization and clinical features of a patient with an interstitial deletion of 3p25.3-p26.1. *Am. J. Med. Genet. A.* 152A: 3110-3114. <https://doi.org/10.1002/ajmg.a.33353>
- Hamdan FF, Gauthier J, Spiegelman D, Noreau A, et al.; Synapse to Disease Group (2009a). Mutations in SYNGAP1 in autosomal nonsyndromic mental retardation. *N. Engl. J. Med.* 360: 599-605. <https://doi.org/10.1056/NEJMoa0805392>
- Hamdan FF, Piton A, Gauthier J, Lortie A, et al. (2009b). *De novo* STXBP1 mutations in mental retardation and nonsyndromic epilepsy. *Ann. Neurol.* 65: 748-753. <https://doi.org/10.1002/ana.21625>
- Kellogg G, Sum J and Wallerstein R (2013). Deletion of 3p25.3 in a patient with intellectual disability and dysmorphic features with further definition of a critical region. *Am. J. Med. Genet. A.* 161A: 1405-1408. <https://doi.org/10.1002/ajmg.a.35876>
- Kobayashi Y, Tohyama J, Kato M, Akasaka N, et al. (2016). High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. *Brain Dev.* 38: 285-292.
- Kuechler A, Zink AM, Wieland T, Lüdecke HJ, et al. (2015). Loss-of-function variants of *SETD5* cause intellectual disability and the core phenotype of microdeletion 3p25.3 syndrome. *Eur. J. Hum. Genet.* 23: 753-760. <https://doi.org/10.1038/ejhg.2014.165>
- Peltekova IT, Macdonald A and Armour CM (2012). Microdeletion on 3p25 in a patient with features of 3p deletion syndrome. *Am. J. Med. Genet. A.* 158A: 2583-2586. <https://doi.org/10.1002/ajmg.a.35559>
- Pinto D, Delaby E, Merico D, Barbosa M, et al. (2014). Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *Am. J. Hum. Genet.* 94: 677-694. <https://doi.org/10.1016/j.ajhg.2014.03.018>
- Rauch A, Wiczorek D, Graf E, Wieland T, et al. (2012). Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. *Lancet* 380: 1674-1682. [https://doi.org/10.1016/S0140-6736\(12\)61480-9](https://doi.org/10.1016/S0140-6736(12)61480-9)

- Riess A, Grasshoff U, Schäferhoff K, Bonin M, et al. (2012). Interstitial 3p25.3-p26.1 deletion in a patient with intellectual disability. *Am. J. Med. Genet. A.* 158A: 2587-2590. <https://doi.org/10.1002/ajmg.a.35562>
- Sowalsky AG, Xia Z, Wang L, Zhao H, et al. (2015). Whole transcriptome sequencing reveals extensive unspliced mRNA in metastatic castration-resistant prostate cancer. *Mol. Cancer Res.* 13: 98-106. <https://doi.org/10.1158/1541-7786.MCR-14-0273>
- Szczałuba K, Brzezinska M, Kot J, Rydzanicz M, et al. (2016). SETD5 loss-of-function mutation as a likely cause of a familial syndromic intellectual disability with variable phenotypic expression. *Am. J. Med. Genet. A.* 170: 2322-2327. <https://doi.org/10.1002/ajmg.a.37832>