# A novel *MYT1L* mutation in a patient with severe early-onset obesity and intellectual disability

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**Abstract**

The genetic background of severe early-onset obesity is still incompletely understood. Deletions at 2p25.3 associate with early-onset obesity and variable intellectual disability. *Myelin-transcriptor-factor-1-like* (*MYT1L)* gene in this locus has been proposed a candidate gene for obesity. We report on a 13-year-old boy presenting with overweight already at 1 year of age (body mass index (BMI) Z-score +2.3) and obesity at 2 years of age (BMI Z-score +3.8). The patient had hyperphagia and delayed neurological, cognitive and motor development. He also had speech delay, strabismus, hyperactivity and intellectual disability. Brain MRI was normal. The parents and sister had normal BMI. Whole-genome sequencing identified in the index patient a novel *de novo* frameshift deletion that introduces a premature termination of translation NM_015025.2(MYT1L): c.2215_2224delACGCGCTGCC, p.(Thr739Alafs*7) in *MYT1L*. The frameshift variant was confirmed by Sanger sequencing. Our finding supports the association of *MYT1L* mutations with early-onset syndromic obesity. The identification of novel monogenic forms of childhood-onset obesity will provide insights to the involved genetic and biologic pathways.

**KEYWORDS*:***

hyperphagia, infancy-onset obesity, *MYT1L*

## INTRODUCTION

Genetic and molecular mechanisms underlying severe obesity are still incompletely understood; to date, disease-causing genes have been identified in only 24% of the syndromic forms of obesity (Kaur, de Souza, Gibson & Meyre, 2017).

Deletions in 2p25.3 have been reported in several patients with intellectual disability and obesity (Bonaglia, Giorda & Zanini, 2014; De Rocker et al., 2015, Doco-Fenzy et al., 2013, Stevens et al., 2011). *Myelin-transcription-factor-1-like* (*MYT1L*) falls within the deleted region and has been proposed as a candidate gene for obesity and intellectual disability (De Rocker et al., 2015). In line with this, a recent study identified *de novo* single nucleotide variants (SNVs) in *MYT1L* in patients with intellectual disability and variable obesity (Blanchet et al., 2017).

MYT1L, encoded by *MYT1L*, belongs to the myelin transcription factor family and is expressed in the developing brain (De Rocker et al., 2015). Although the exact functions in the brain are unclear, MYT1L is known to regulate neuronal differentiation by repressing expression of non-neuronal genes and negative regulators of neurogenesis, and inducing pro-neuronal genes (Kepa et al., 2017; Mall et al., 2017).

We present a boy with intellectual disability, hyperphagia and severe early-onset obesity. Whole-genome sequencing (WGS) of the patient and his first-degree relatives identified a novel *de novo* frameshift deletion p.(Thr739Alafs*7) in *MYT1L* in the index patient.

## CLINICAL REPORT

This study was approved by the Institutional Research Ethics Committee and a written informed consent was obtained from all study participants and in case of minors, from their legal guardians. The index patient is a 13-year-old boy who was born at 37 weeks of gestation to unrelated healthy parents of Finnish descent. Pregnancy and delivery were uncomplicated

and birth measurements were normal: weight of 3.38 kg (+0.1 SD), length 50 cm (+0.1 SD) and OFC 33 cm. Already at 12 months he was overweight with weight 12.2 kg (+2.2 SD) and length 77.6 cm (+0.8 SD) (body mass index (BMI) 20.3 kg/m$^2$, BMI Z-score +2.3) and by 2 years his BMI Z-score had increased to +3.8 (weight +3.5 SD, length +1.1 SD) (Figure 1a). Parents reported hyperphagia, food seeking behavior, and impaired satiety. Presently at the age of 13.8 years, he is obese with weight 82.1 kg and height 163.1 cm (BMI 31 kg/m$^2$, BMI Z-score +2.8), (Figure 1b), and waist circumference 104.5 cm. His parents have normal weight (mother's BMI 23 kg/m$^2$ and father's 25 kg/m$^2$). His 9-year-old sister has normal BMI (Z score +1.6) and normal development.

In addition to severe obesity, his neurological, cognitive and motor development were delayed. He presented with delayed speech, clumsiness, problems with balance, and strabismus. He was diagnosed with attention deficit and hyperactivity but had no aggressive behavior. He did not present with any dysmorphic features. Brain MRI at 4 years was normal and showed no hypothalamic or pituitary pathology. An electroencephalography EEG was also normal. He attends a special needs school.

Laboratory investigations during childhood excluded hypothyroidism, hypercortisolism, and metabolic abnormalities. Fasting blood concentrations of glucose, insulin, cholesterol, and triglycerides were within normal range. Karyotype and screening for Prader-Willi and Fragile-X syndromes were normal.

Array comparative genomic hydridization (aCGH) analysis was performed and no copy number variants (CNVs) that could explain the phenotype were detected. We performed WGS on genomic DNA from the index, both parents and the healthy sibling. Sample library preparation, sequencing, and primary bioinformatics were performed at the Science for Life Laboratory, Stockholm. Analysis of raw data was done as previously described (Costantini et al., 2018). We filtered variants that fit into *de novo*, compound heterozygous or autosomal

recessive inheritance pattern and excluded variants with allele frequency of 0.5% and higher in 1000 Genomes Project (http://www.internationalgenome.org), Exome Aggregation Consortium (http://exac.broadinstitute.org), the Genome Aggregation Database (http://gnomad.broadinstitute.org), the SweGen dataset for genetic variations in the Swedish population (https://swegen-exac.nbis.se), and the Sequencing Initiative Suomi project (SISu) for genetic variants in the Finnish population (http://sisuproject.fi). We only included nonsynonymous variants, indels, and putative splice site variants for further consideration. The potential pathogenicity of the variants was assessed with Combined Annotation Dependent Depletion (CADD), polymorphism phenotyping (PolyPhen), sorting intolerant from tolerant (SIFT) prediction scores, and MutationTaster2.

The WGS data analysis identified a novel heterozygous *de novo* frameshift deletion NM_015025.2(MYT1L): c.2215_2224delACGCGCTGCC, p.(Thr739Alafs*7) in exon 15 of *MYT1L* (Figure 2a,b). We confirmed the frameshift mutation with Sanger sequencing (Figure 2c). The mutation was absent in the parents and sibling (Figure 2d). This frameshift variant has not been previously reported in the above-mentioned databases but is found in 1 out of the 8696 in the African population in Genome Aggregation Database gnomAD (http://gnomad.broadinstitute.org). MutationTaster2 predicted the deletion as disease-causing. No other potential disease-causing variants were identified for the assumed inheritance patterns.

## DISCUSSION

We describe a novel *de novo MYT1L* mutation in a patient with early-onset obesity, hyperphagia, developmental delay, and intellectual disability. Our case report supports the role of *MYT1L* mutations in syndromic obesity.

Deletions of 2p25.3 disrupting *MYT1L* have been reported in several patients sharing clinical features like overweight/obesity, hyperphagia, intellectual disability, behavioral

problems, and some dysmorphic features (Bonaglia et al., 2014; De Rocker et al., 2015; Doco-Fenzy et al., 2013; Stevens et al., 2011). Exome sequencing recently revealed nine *MYT1L* mutations in patients with variable intellectual disability and obesity (Blanchet et al., 2017). All nine patients with *MYT1L* SNVs reported by Blanchet et al. (2017) had intellectual disability or developmental delay, six patients had obesity and three patients presented with autism spectrum disorder. Blanchet et al. (2017) performed a careful comparison of the clinical manifestations in patients with CNVs involving *MYT1L* and patients with SNVs in *MYT1L* and they observed no difference between patients with CNVs or SNVs in respect to obesity/overweight, hyperphagia, intellectual disability, autism, gross motor delay and speech delay.

Our patient has a similar phenotype as patients with 2p25.3 deletions features (Bonaglia et al., 2014; De Rocker et al., 2015; Doco-Fenzy et al., 2013; Stevens et al., 2011). or *MYT1L* SNVs (Figure 2a,b) (Blanchet et al., 2017). However, the first symptom in our patient was early-onset obesity starting already before the age of 2 years and continuing with increasing BMI Z-score up to the age of 10 years. Thereafter the patient's BMI has to some extent stabilized, possibly because of the parents' intense restriction of food intake despite persisting food seeking behavior and insatiable hunger. Besides obesity, our patient presented with developmental delay, intellectual disability and hyperactivity but brain MRI showed no pathology.

MYT1L is expressed in neuronal tissues and the expression is high during fetal brain development (De Rocker et al., 2015). Several obesity genes are involved in the brain's neuroendocrine satiety system and the hypothalamic leptin-melanocortin-SIM1 pathway is affected in many monogenic obesity disorders (Kaur et al., 2017). Interestingly, Blanchet et al. (2017) recognized MYT1L as part of the leptin-melanocortin-SIM1 pathway and oxytocin (OXT) downstream of *MYT1L* and identified *OXT* as an important factor in obesity

pathogenesis. Loss of *MYT1L* in experimental zebrafish was related to impaired development of hypothalamus and reduced expression of oxytocin in the brain, providing a possible pathogenetic explanation for the syndromic obesity.

Genetics are acknowledged to contribute to childhood-onset obesity and several monogenic forms of obesity or syndromic disorders with obesity have been described (Kaur et al., 2017). Severe childhood-onset obesity poses diagnostic and treatment-related challenges. Early intervention and diagnosis is warranted in pediatric patients with early-onset severe obesity and genetic causes should be considered. The Endocrine Society recommends genetic testing in patients with obesity onset before 5 years of age and clinical manifestations of genetic obesity syndrome and/or severe obesity in family (Styne et al., 2017). Identification of the genetic causes underlying obesity will advance future therapeutic means, support patients against social stigmata of obesity and enable genetic counselling.

## CONCLUSIONS

We report on a novel frameshift variant in *MYT1L* as the cause of early childhood-onset obesity with hyperphagia and intellectual disability. Our finding further strengthens the hypothesis that *MYT1L* is a candidate gene for syndromic obesity. The identification of new candidate genes for severe obesity will provide insights to the pathogenic mechanisms involved in early-onset severe obesity. Further studies on MYT1L are warranted to expand our understanding of its biological function, role in appetite regulation and development of the syndromic features, and to identify novel therapeutic targets.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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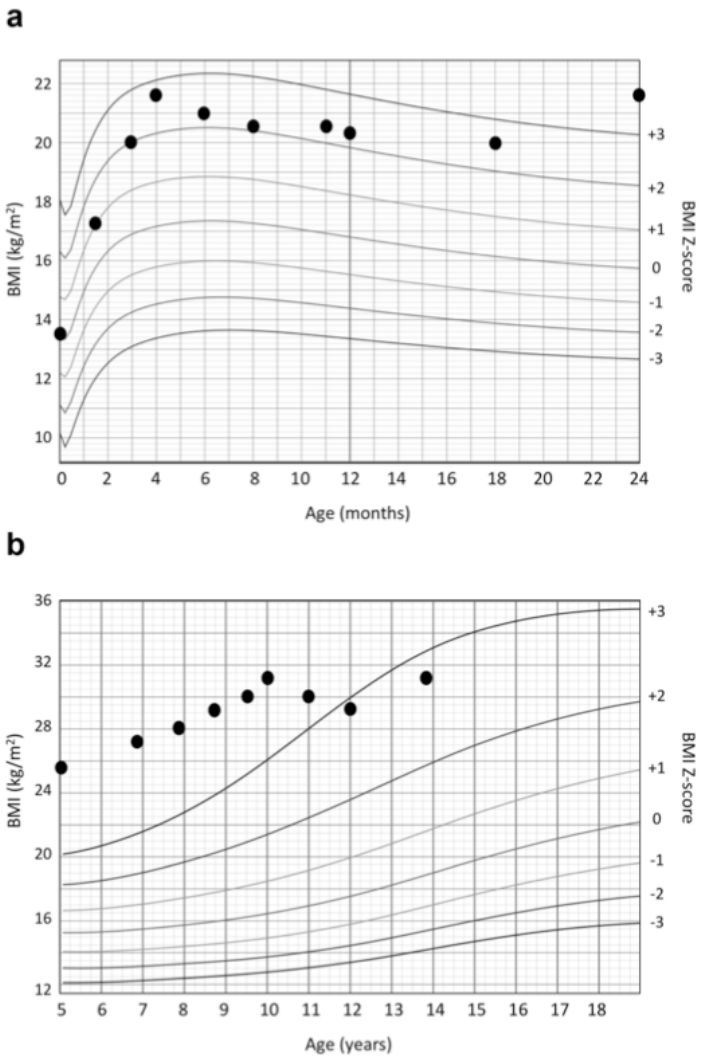


**FIGURE 1** The patient's BMI for age at 0-2 years (a) and 5-19 years (b). The BMI Z-scores have been calculated according to WHO Child Growth Standards (www.who.int/childgrowth/standards).

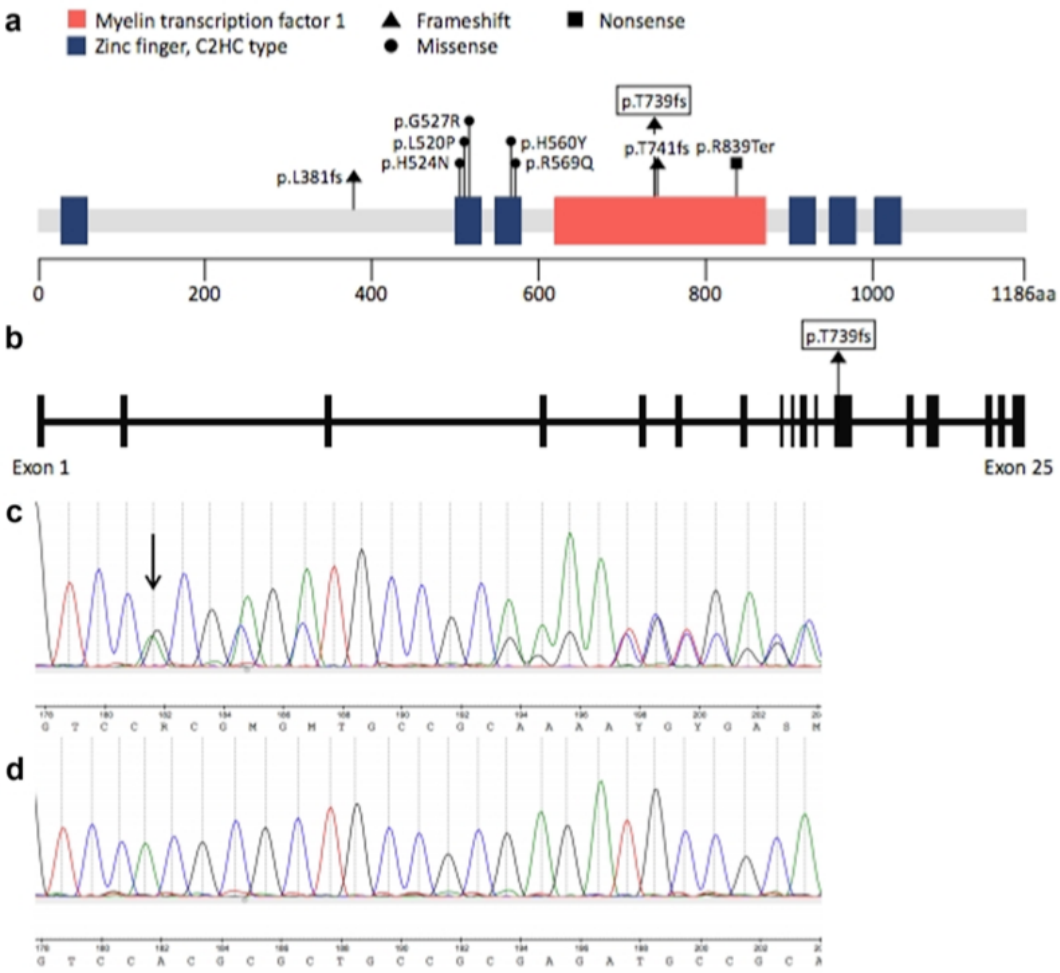


**FIGURE 2** (a) Schematic illustration of the MYT1L protein showing the protein's different domains, previously reported pathogenic variants (Blanchet et al., 2017), and the location of the variant found in our patient. (b) Schematic illustration of the MYT1L gene showing the patient's variant in exon 15. (c) Chromatograms of a direct sequence analysis of *MYT1L* gene exon 15 showing a novel heterozygous *de novo* frameshift deletion c.2215_2224delACGCGCTGCC, p.(Thr739Alafs*7) in a 13-year-old boy with severe obesity and intellectual disability. His healthy parents and sister had normal *MYT1L* sequences (d).