

CASE REPORT

MYT1L mutation in a patient with severe early-onset obesity and intellectual disability

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ABSTRACT

Children suffering from intellectual disability, dysmorphic features and organ-specific developmental abnormalities should undergo genetic testing. Entities such as X fragile syndrome should be investigated. If we add obesity to the “equation”, Prader-Willi and Bardet-Biedl are thus far the most common syndromic conditions to be found. The evolution of genetic testing brought several other genetic determinants of developmental delay. We report on a 4-year-old girl presenting with obesity and delayed neurological, cognitive and motor development whose genetic testing by array-based comparative genomic hybridization exposed a partial deletion at chromosome 2p25.3, containing the gene *MYT1L*.

KEY WORDS:

MYT1L, global developmental delay, neurodevelopment, obesity.

INTRODUCTION

Global developmental delay (GDD) is the term used to describe developmental disability in children under the age of five. Global developmental delay is defined as a delay in two or more developmental domains of gross/fine motor, speech/language, cognition, social/personal and activities of daily living and is seen as a temporary diagnosis for children who are unable to undergo standardized intelligence quotient (IQ) evaluation. The global developmental delay incidence rate is in the range 1–3% in school-age children [1, 2]. Obesity is defined as having a body mass index of over the 95th centile in children and affects 5–12% of children aged under 5 years in western European countries [3]. Both obesity and GDD are major public health concerns in Western countries. Syndromic obesity refers to cases of obesity that also have other phenotypes, such as intellectual disability (ID), dysmorphic characteristics, or developmental disorders. These conditions are not only rare but highly variable. A Mendelian pattern of inheritance is pres-

ent in a large proportion of these patients and may result from altered gene expression with pleiotropic effects [4]. Even though these genes are frequently autosomal or X-linked, in most cases their origin is unknown. The most well-known hereditary syndromes in which obesity is a key trait are Prader-Willi and Bardet-Biedl; however, there are many other conditions of syndromic obesity identified in the literature including Kleefstra type 1, MORM (mental retardation, truncal obesity, retinal dystrophy and micro penis), Alström, and Cohen syndromes, amongst others [5]. Recently Stevens [6] reported a potential association between *MYT1L* haploinsufficiency and obesity. *MYT1L* is a gene member of the myelin transcription factor family and is involved in neurogenesis, being highly transcribed in the mouse embryonic brain and essential for inducing functional mature neurons [7–9]. After the description of a rare cytogenetic aberration, partial deletion of chromosome band 2p25.3, in patients with ID, Stevens defined a smaller region of overlap in patients with ID. All patients, 6, with ID were also overweight/obese.

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The index patient is a 4-year-old girl who was born at 39 weeks of gestation to unrelated self-proclaimed healthy parents of Portuguese descent. On the paternal side there is a record of difficulties learning including the grandfather and the father himself. The father, 32 years old, has been said to be intellectually impaired, though not objectively documented, analphabet, and he is obese. The mother is 44 years old, finished 6th grade and is also obese. Pregnancy and delivery were uncomplicated and birth measurements were normal: weight of 2.88 kg ($p = 29.7$), length of 48 cm ($p = 11$) and occipital frontal circumference 34.5 cm ($p = 25$). According to the medical records, due to jaundice occurring in the neonatal period, 4 days of phototherapy were administered. At day 28 of life, she was admitted for antibiotherapy caused by omphalitis. Regarding the social and school background, this child was cared for and educated at home until the age of 4, only then attending a pre-school. That same pre-school identified difficulties in toilet training, motor incoordination in a task and when playing with her friends, eventually harming them unintentionally, and aggressive behavior when displeased. Evoked auditory potentials elicited normal results except hearing loss. On physical examination the following features were noted: macro-somic overall look, macroglossia, open bite, orofacial hypotonia, hypertelorism, flat nose base, short neck, pectus excavatum, dental hypoplasia, blurred nasolabial fold and large intermammary distance. Heart sounds were normal. No palm crease, umbilical hernia or cutaneous spots were present. Abdominal examination was also ordinary and no malformations were found. Her weight and body mass index were above 2 standard deviations for that age and gender. A protocol study of GDD was conducted with the approval of the parents including metabolic and biochemical tests and genetic comparative genomic hybridization (CGH). The former included blood samples: full blood count, urea and electrolytes, thyroid function tests, creatine kinase, liver function test, amino acids, creatine and lipid panel. Urine samples were used for the study of glycosaminoglycans and organic acids. The results of all of these tests were normal. As to the latter, the CGH displayed a partial deletion at chromosome 2p25.3 (127771-3063919), the size of 3.05 Mb, encompassing the *MYT1L* gene. Both parents were genetically studied using the following methods: karyotype, GTL banding, subtelomeric FISH and MLPA. No abnormal mutations were found at chromosome 2p25.3 and karyotypes were 46 XX and 46 XY, respectively for the mother and father. Consequently, a *de novo* 3.05 Mb deletion of 2p25.3 in a girl with distinctive phenotype, early-onset obesity and ID was identified, supporting the idea that subtelomeric 2p25.3 deletion is linked with syndromic obesity.

DISCUSSION

We report on a *de novo* deletion variant in *MYT1L* as the cause of early childhood-onset obesity with hyperphagia and GDD, raising to 63 the number of reports published in the literature regarding patients with *MYT1L*-associated neurodevelopmental disorders. Coursimault *et al.* [10] described developmental delay and language impairment as the most common features (95%) in *MYT1L* haploinsufficiency. Early onset overweight/obesity (59%) and eating behavioral disorders including hyperphagia (45%) were also very common. Less frequently found disorders were epilepsy (29%) and sleeping disorders. As to craniofacial dysmorphic features present in patients with *MYT1L* mutations, they were reported to be non-specific and inconsistent, including almond-shaped eyes with enophthalmos, a bulbous nose with slightly anteverted nostrils, full and sagging cheeks and a marked cupid's bow of the upper lip. Macrocephaly, strabismus and hand/feet malformations are also recurrent features of *MYT1L* mutations [9].

Patients with *MYT1L* mutations fall within a wide phenotypic spectrum, but the differential diagnosis of cases of GDD/intellectual impairment and early-manifestation obesity should take *MYT1L* mutations into consideration along with other etiologies, such as Prader-Willi or Bardet-Biedl. Comprehensive clinical assessment remains the core for planning investigations in young children presenting with GDD, but the importance of genetic testing should not be dismissed. The description of this syndrome is due to the development of genetic testing in recent years associated with the ease of sharing and interpreting massive amounts of data. Evidence-based international guidelines all promote the use of chromosome array as a first-tier investigation for GDD, along with metabolic and biochemical (urine and blood samples) tests, if no etiological indicators from history and examination were found. Once a diagnosis has been made clinicians can specify treatment options, monitor for known consequences, and offer prognosis and condition-specific family assistance (including family planning options). This guarantees the best possible outcomes for the children, their families, and their caregivers. Additionally, a diagnosis can prevent medical professionals from moving on to possibly more costly and intrusive investigations and can offer parents an explanation, closure, or sense of acceptance.

CONCLUSIONS

More research on *MYT1L* to better understand its biological role, involvement in appetite regulation, role in the emergence of syndromic characteristics, and to find new treatment targets is needed.

DISCLOSURES

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3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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