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ORIGINAL INVESTIGATION

MYT1L-associated neurodevelopmental disorder: description of 40 new cases and literature review of clinical and molecular aspects

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Abstract
Pathogenic variants of the myelin transcription factor-1 like (*MYT1L*) gene include heterozygous missense, truncating variants and 2p25.3 microdeletions and cause a syndromic neurodevelopmental disorder (OMIM#616,521). Despite enrichment in de novo mutations in several developmental disorders and autism studies, the data on clinical characteristics and genotype–phenotype correlations are scarce, with only 22 patients with single nucleotide pathogenic variants reported. We aimed to further characterize this disorder at both the clinical and molecular levels by gathering a large series of patients with *MYT1L*-associated neurodevelopmental disorder. We collected genetic information on 40 unreported patients with likely pathogenic/pathogenic *MYT1L* variants and performed a comprehensive review of published data (total = 62 patients). We confirm that the main phenotypic features of the *MYT1L*-related disorder are developmental delay with language delay (95%), intellectual disability (ID, 70%), overweight or obesity (58%), behavioral disorders (98%) and epilepsy (23%). We highlight novel clinical characteristics, such as learning disabilities without ID (30%) and feeding difficulties during infancy (18%). We further describe the varied dysmorphic features (67%) and present the changes in weight over time of 27 patients. We show that patients harboring highly clustered missense variants in the 2–3-ZNF domains are not clinically distinguishable from patients with truncating variants. We provide an updated overview of clinical and genetic data of the *MYT1L*-associated neurodevelopmental disorder, hence improving diagnosis and clinical management of these patients.

Introduction

The MYT1L protein is encoded by the *MYT1L* gene, also called *NZF-1*. It belongs to the family of myelin transcription factors, together with MYT1 (or NZF-2) and ST18 (or NZF-3) (Jiang et al. 1996). This transcription factor contains six characteristic zinc finger (ZNF) domains (one N-terminal zinc finger, two tandem central zinc fingers and three C-terminal zinc fingers) with a unique cysteine-cysteine-histidine-cysteine (CCHHC) consensus DNA binding sequence. Its expression pattern is best characterized in a subset of neural progenitors in distinct regions of the central nervous system, particularly the cortex (Jiang et al. 1996; Kim et al. 1997; Matsushita et al. 2014). Expression levels appear to

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peak during fetal development in both animal models and in humans but also continue into larval/pre-weaning stages in rodents and fish, implying that transcription may also persist in children's brains (Kim et al. 1997; De Rocker et al. 2015). *MYT1L* plays a pivotal role in neurogenesis in the transformation of neural stem cells into mature neurons and in the differentiation and proliferation of oligodendrocyte precursor cells (Shi et al. 2018), which are essential for myelination and remyelination of the central nervous system (CNS) (Jiang et al. 1996; Kim et al. 1997). Interestingly, *MYT1L* cooperates with other transcription factors in the in vitro conversion of fibroblasts into functional neurons (Vierbuchen et al. 2010). *MYT1L* acts as a transcriptional repressor of non-neuronal genes, mediated through the recruitment of a complex containing Sin3b, by binding to the 5′–AAGTT–3′ motif present in the promoter of its target genes (and absent from the promoters of neuronal genes) (Romm et al. 2005; Mall et al. 2017; Manukyan et al. 2018). In addition, the involvement of *MYT1L* in appetite regulation and predisposition to overweight/obesity has been studied in zebrafish knockdown models, suggesting that *MYT1L* may play a role in regulating the development of the neuroendocrine hypothalamus through the leptin-melanocortin-SIM1 pathway (Blanchet et al. 2017).

The association of *MYT1L* with neurodevelopmental disorders (NDD) in humans (OMIM #616,521) was described in 2011 with the observation that overlapping 2p25.3 deletions encompassing *MYT1L* in 6 patients shared intellectual disability (ID), obesity or overweight and dysmorphic facial features (Stevens et al. 2011). Subsequently, microarray-based analysis identified additional patients, leading to a better clinical understanding of this chromosomal disorder (Becker et al. 2010; Rio et al. 2013; Bonaglia et al. 2014; Doco-Fenzy et al. 2014; Tu et al., 2014; De Rocker et al. 2015; Mayo et al. 2015; Vlaskamp et al. 2017; D'Angelo et al. 2018, Mansfield et al. 2020). The identification of de novo truncating single nucleotide variants (SNVs) in two patients with an overlapping phenotype further implicated haploinsufficiency of *MYT1L* as the cause of the phenotype associated with 2p25.3 deletions (de Ligt et al. 2012; De Rocker et al. 2015). In 2017, Blanchet et al. published a comprehensive series of nine novel patients with nucleotide-level *MYT1L* variants and compared the clinical pictures of SNV mutation carriers with that of microdeletion carriers (Blanchet et al. 2017). Subsequently, 11 additional patients with SNVs have been described with clinical data and comparison with individuals harboring *MYT1L* large deletions revealed no significant difference in the main clinical features (Wang et al. 2016; Loid et al. 2018; Al Tuwaijri and Alfadhel 2019; Windheuser et al. 2020; Carvalho et al. 2021). Furthermore, while *MYT1L* haploinsufficiency has been associated with NDD, partial duplications of *MYT1L* have been suggested as responsible of a distinct phenotype with schizophrenia (Mansfield et al. 2020). However, the precise molecular mechanisms underlying this phenotype remain elusive.

In a genomic approach, several trio-based exome/genome studies identified a significant enrichment in de novo *MYT1L* mutations in patients with NDD and autism (De Rubeis et al. 2014; Sanders et al. 2015; Deciphering Developmental Disorders Study 2017; Satterstrom et al. 2020; Kaplanis et al. 2020). These strong statistical signals contrasted with the paucity of clinical descriptions in the literature. We therefore aimed to further characterize this disorder at both the clinical and molecular levels by gathering and analyzing a large series of patients with *MYT1L*-associated neurodevelopmental disorder.

Materials and methods

Patient recruitment

Forty patients with likely pathogenic and pathogenic (LP/P) *MYT1L* variants were gathered through data sharing resources including Genematcher (Sobreira et al. 2015), the French national AnDDi-Rares network and the GeneDx laboratory. Each patient received a sequencing test in the context of neurodevelopmental abnormalities and/or obesity, either by NGS gene panel, exome or genome sequencing. Clinical and molecular information was collected for all patients consisting of qualitative and quantitative clinical elements, as well as photographs. Notably, the presence or absence and quantification of ID was established either subjectively by the patient's clinician or objectively with an IQ test. This aspect is specified for each patient in supplementary data. The IQ norms used were as follows: no ID (full scale IQ greater than 70), mild ID (50–69), moderate ID (35–49), severe ID (20–34). The BMI curves were established from the latest curves from the French Association of Ambulatory Pediatrics (updated in 2019). The criteria for establishing the clinical diagnosis of microcephaly were a head circumference of less than -2SD, while the criteria for establishing the clinical diagnosis of macrocephaly were a head circumference greater than + 2SD. All patients or legal guardians provided informed written consent for genetic analyses. Patients or legal guardians have given their consent for their photograph to appear in the publication. This study has been approved on 01/15/2020 by the IRB of Rouen University Hospital, France, approval n°69–2020. The patients described in this study had not been previously reported in the literature.

The inclusion criteria in our study were: (i) presence of an heterozygous truncating variant, i.e. any SNV/indel introducing a premature stop codon or disrupting a canonical splice site, whatever the inheritance status or (ii) an

already described pathogenic non-truncating variant, whatever the inheritance status, or (iii) presence of a de novo heterozygous missense variant with a predicted deleterious by the SIFT, Polyphen2 and MutationTaster bioinformatics tools, and absent from gnomAD v2.1 (Karczewski et al. 2020). *MYT1L* variants were annotated following the NM_015025.4 transcript (1184 residues). In total, 40 patients were included, from France, Belgium, Luxembourg and the United States of America.

Literature review

We performed a comprehensive PubMed search with the terms "MYT1L" and "2p25.3" and manually assessed articles to identify those reporting cases of SNVs/indels in patients. Only articles with clinical description and LP/P variant were retained. A total of 22 patients with SNVs/indels were included in this study, representing a total of eight articles (de Ligt et al. 2012; De Rocker et al. 2015; Wang et al. 2016; Blanchet et al. 2017; Loid et al. 2018; Al Tuwaijri and Alfadhel 2019; Windheuser et al. 2020; Carvalho et al. 2021).

Statistical analyses

First, we assessed whether or not missense variants clustered more than expected by chance. We performed a permutation test following the method described in Lelieveld et al. (2017) (Lelieveld et al. 2017).

Then, to assess if missense variants were present in our cohort cluster within the second and third zinc-finger (2–3-ZNF) domains, we performed an exact binomial test to compare the proportion of missense variants observed within the 2–3-ZNF domains to the expected proportion (π_0) under a uniform distribution of missense variants along the coding region (π_0 = 88/1184 = the number of residues within the 2–3-ZNF domains / the total number of residues within the gene). Then, we assessed whether the proportion of missense variants within the 2–3-ZNF domains differs from the proportion of truncating variants included in these domains using a Fisher exact test.

We merged literature data and our cohort to compare phenotypes of carriers of heterozygous truncating variants (N = 40) to carriers of heterozygous missense variants (N = 19). Forty-one phenotypes were analyzed separately using a χ^2 test or a Fisher's exact test when conditions for χ^2 test were not met. Threshold for significance at level 5% after Bonferroni correction is set to 0.0012.

We also performed a multiple linear mixed effect model to assess the evolution of BMI according to age, type of variant and age*type of variant interaction. Data were censored and thus interpreted until 18-years old to overcome the lack of data at older ages. The model was adjusted for sex as fixed effect and for individual identifier (intercept and slope) as random effects.

All statistical tests were two-tailed and performed with R software (version 3.4.2, https://www.r-project.org/).

Results

We collected clinical and molecular data from 40 patients with LP/P variants (SNV or indels) in the *MYT1L* gene. Thirty-six variants arose de novo, two were inherited from a symptomatic parent who were not included in this study due to a lack of clinical information, and two were not inherited from one parent while the other was not available for testing. Mother of P5 presented no motor delay but received specific care in an adapted school and then sheltered employment. She can read and write a little, and may have a mild intellectual disability, of which we have no details. She is overweight (height 165 cm for 75 kg). The cranial perimeter is 53,5 cm (mean). Father of P33 is described as having developmental issues and is overweight. Variants included fourteen missense, thirteen frameshift indels, eight nonsense, four splice variants and one single exon deletion (See Fig. 4).

Description of a series of 40 patients with *MYT1L*-associated neurodevelopmental disorder

Patients' ages ranged from 1.6 to 34 years (median 8.4 years) at last visit. Of the 40 patients included, 18 were female (45%). Patients were referred to clinical geneticists or pediatricians for developmental delay, ID, epilepsy and/or obesity. Fourteen patients were diagnosed through a neurodevelopmental disorders gene panel, 25 patients by singleton or trio-based exome sequencing and one with whole genome sequencing. The phenotypic data of these 40 novel patients harboring a LP/P *MYT1L* variant, together with data from 22 SNV/indel patients from the literature, are summarized in Table 1 and Supplementary tables 1–3, and further described in the next sections.

Pregnancy and neonatal period

Pregnancies were marked by complications of varying severity and low specificity in 12/40 patients: gestational diabetes, decreased fetal active movements, intrauterine growth restriction (IUGR), intrapartum hemorrhage, gestational hypertension, and threat of preterm delivery. Three children were reported with organ malformations: renal cysts in P7, a right diaphragmatic dome hernia diagnosed at 23 weeks of gestation in P29 and a moderate unilateral cerebral ventriculomegaly in P40. Thirty-five (90%) patients

Table 1 Clinical features of the 40 individuals of the cohort and previously published *MYT1L* SNV/indel patients

	Phenotype	Our study ($n=40$)	Previously published patients with SNVs/indels[1] ($n=22$)
Neonatal period	Sex (%F)	45% (18/40)	50% (11/22)
	Complicated pregnancy	30% (12/40)	19% (4/21)
	Term (> 37 weeks of gestation)	90% (35/39)	95% (20/21)
	Eutrophic (weight 10–90 percentile)	92% (34/37)	94% (17/18)
	Neonatal hypotonia	15% (6/39)	42% (8/19)
	Early neonatal disorders	40% (16/40)	26% (5/19)
	Organ malformations	8% (3/40)	14% (3/21)
	Neonatal eating disorders	18% (7/40)	11% (2/19)
	Gastroesophageal reflux neonatal	13% (5/40)	11% (2/18)
Development	Motor delay	78% (31/40)	90% (19/21)
	Fine motor disorder	81% (26/32)	90% (9/10)
	Global hypotonia in childhood	47% (18/38)	68% (13/19)
	Language delay	95% (38/40)	95% (20/21)
	Intellectual disability	70% (21/30)	100% (20/20)
	Mild	24% (5/21)	30% (6/20)
	Moderate	43% (9/21)	15% (3/20)
	Severe	19% (4/21)	0% (0/20)
	ID of non-specified severity	14% (3/21)	55% (11/20)
	Learning difficulties without ID	30% (9/30)	0% (0/20)
	Specialized education	94% (34/36)	100% (10/10)
	Para-medical support	94% (34/36)	100% (1/1)
Neurology/behavior	Behavioral disorders	98% (39/40)	90% (19/21)
	ASD, formal or informal diagnosis	43% (17/40)	43% (9/21)
	Stereotypies	55% (22/40)	19% (4/21)
	Self- or hetero-aggressiveness	45% (18/40)	38% (8/21)
	Intolerance to frustration	53% (21/40)	19% (4/21)
	ADHD	38% (15/40)	48% (10/21)
	Anxiety	25% (10/40)	10% (2/21)
	Cheerful behavior	18% (7/40)	10% (2/21)
	Epilepsy	23% (9/40)	29% (6/21)
	Brain MRI abnormalities	28% (8/29)	31% (5/16)
Weight disorder	Overweight/obesity	58% (23/40)	59% (13/22)
	Overweight (BMI 25–29.9)	23% (9/40)	23% (5/22)
	Obesity (BMI > 30)	35% (14/40)	36% (8/22)
	Standard weight (BMI 18.5–24.9)	43% (17/40)	41% (9/22)
	Eating behavior disorder	45% (18/40)	48% (10/21)
	Failure to thrive	18% (7/40)	0% (0/22)
Others	Sleep disorders	33% (13/40)	28% (5/18)
	Ophthalmological abnormalities	30% (12/40)	53% (9/17)
	Short stature (< -2 SD)	8% (3/40)	0% (0/20)
	Endocrine disorders	10% (4/39)	18% (2/11)
	Lipid abnormalities	3% (1/39)	9% (1/11)
	Dysmorphism	67% (26/39)	47% (9/19)
	Macrocephaly (> + 2SD)	3% (1/38)	17% (3/18)
	Microcephaly (< −2SD)	11% (4/38)	6% (1/18)
	Tested for Prader–Willi syndrome	68% (15/22)	35% (7/20)

ID intellectual disability, *MRI* magnetic resonance imaging, *N/A* not available, *ASD* autism spectrum disorder, *ADHD* attention deficit hyperactivity disorder, *SD* standard deviation

[a]Blanchet et al. (2017), Windheuser et al. (2020), Al Tuwaijri et Alfadhel (2019), Loid et al. (2018), Carvalho et al. (2021), Wang et al. (2016)

were born at term (> 37 weeks of gestation) and 92% had birth weights between the 10th and 90th percentiles. Two pregnancies were twin pregnancies, marked by low birth weight but the other dizygotic twins did not show any developmental abnormalities. Neonatal hypotonia was observed in 15% of cases. Other non-specific and various neonatal symptoms were identified in 40% of cases such as: early onset of abnormal movements, neonatal torticollis, hypoglycemia, abnormally quiet behavior, oromotor problems, poor eye contact, and respiratory distress.

Neurodevelopmental features

Seventy-eight percent of the patients had a motor delay. The median age of sitting acquisition was 11.5 months and the median age of independent walking was 22 months (Supplementary table 3). Fine motor difficulties were identified in 81% cases. Forty-seven percent of the patients had persistent hypotonia in childhood. Speech delay was evident in 95% of the participants. Language delay was usually reported as severe, with a median for first spoken words at 2.3 years of age, and at 5.0 years for first sentences. Some patients had a major phonological disorder in childhood, with unintelligible jargon and monosyllables. Older patients often spoke with short and simply constructed sentences. Some patients acquired reading and writing abilities, but with limited capabilities. This global psychomotor delay evolved in 70% (21/30) of patients to intellectual disability (ID) of varying severity while 30% (9/30) of patients eventually demonstrated cognitive difficulties without meeting ID criteria or with IQ at the threshold according to current standards. Ten patients could not be cognitively evaluated because of their young age and could not be included in the intellectual impairment calculations, although they all had developmental delay. Among patients with ID, 24% (5/21) were assessed as having mild intellectual impairment, moderate impairment in 43% (9/21) and severe impairment in 19% (4/21). Three patients had ID of unspecified severity. All 9 patients not fulfilling the ID criteria (P3, P10, P11, P23, P25, P26, P29, P34, P40) had learning disabilities, sometimes identified at pre-school age. The absence of significant intellectual impairment had been established by neuropsychological testing or alternatively by the clinical assessment of referring physicians. Many patients appeared to have good lexical stock and verbal comprehension, with lower scores in visuospatial skills, processing speed and working memory. Constraints in orofacial and phonological praxis were frequently noted in association with these difficulties. Visio-attentional disorders were also considered as putative comorbid factors by the physicians. Ninety-four percent of the patients benefited from adapted schooling, generally from the time they entered school. Almost every patient (34/36) was treated from childhood in multidisciplinary rehabilitation (occupational, physical or speech therapy). Two adult patients lived in an occupational home and one worked in a protected sector.

Neurological abnormalities

Nine out of forty participants (23%) were followed for variable types of epilepsy, starting in the neonatal period or during childhood. These included febrile seizures, absence epilepsy, focal epilepsy, and/or tonic–clonic seizures, as well as epileptic foci on an electroencephalogram (P13, P25). Eight patients presented with coordination problems with a slightly unsteady gait. Abnormal brain imaging was seen in 28% of the 29 patients who underwent brain magnetic resonance imaging (MRI). Nonspecific white matter hyperintensities were noted in four patients (14%), ventricular dilatation in 2 (7%), a cyst in the posterior fossa in one (3%), and a thin and dysmorphic corpus callosum as well as delayed myelination in another patient. Four patients had microcephaly (< -2SD) while one patient was macrocephalic (> + 2SD).

Behavioral disorders

All participants presented with behavioral disorders of varying severity. The main symptoms are summarized in Fig. 1. Of the 40 individuals, 17 were affected (43%) with autism spectrum disorder (ASD). Stereotypies were reported in 55% (22/40) of patients, some with and some without an ASD. Forty-five percent of participants (18/40) exhibited self-harming behavior and/or hetero-aggressiveness which could be manifested by self-mutilation of the hands, head banging against walls, biting on the wrists, and occasional aggressiveness towards those around them. Fifty-three percent (21/40) of the patients showed impulsivity or intolerance to frustration. Temper tantrums were reported as intense and exaggerated and could be sometimes linked with food issues. In addition, attention deficit hyperactivity disorder was present in 38% (15/40) of the patients and anxiety in 25% (10/40). Cheerful behavior in everyday life was reported in 18% (7/40). Finally, some patients presented with bruxism in childhood, disinhibition, and recklessness with lack of appreciation of danger, nervous tics, obsessive–compulsive disorder (OCD) or polyembolokoilamania (mainly inserting objects into the external ear canal).

Eating disorders

Gastroesophageal reflux was noted in 13% (5/40) of the children in the neonatal period. Early feeding difficulties, such as poor sucking and slow drinking, were identified

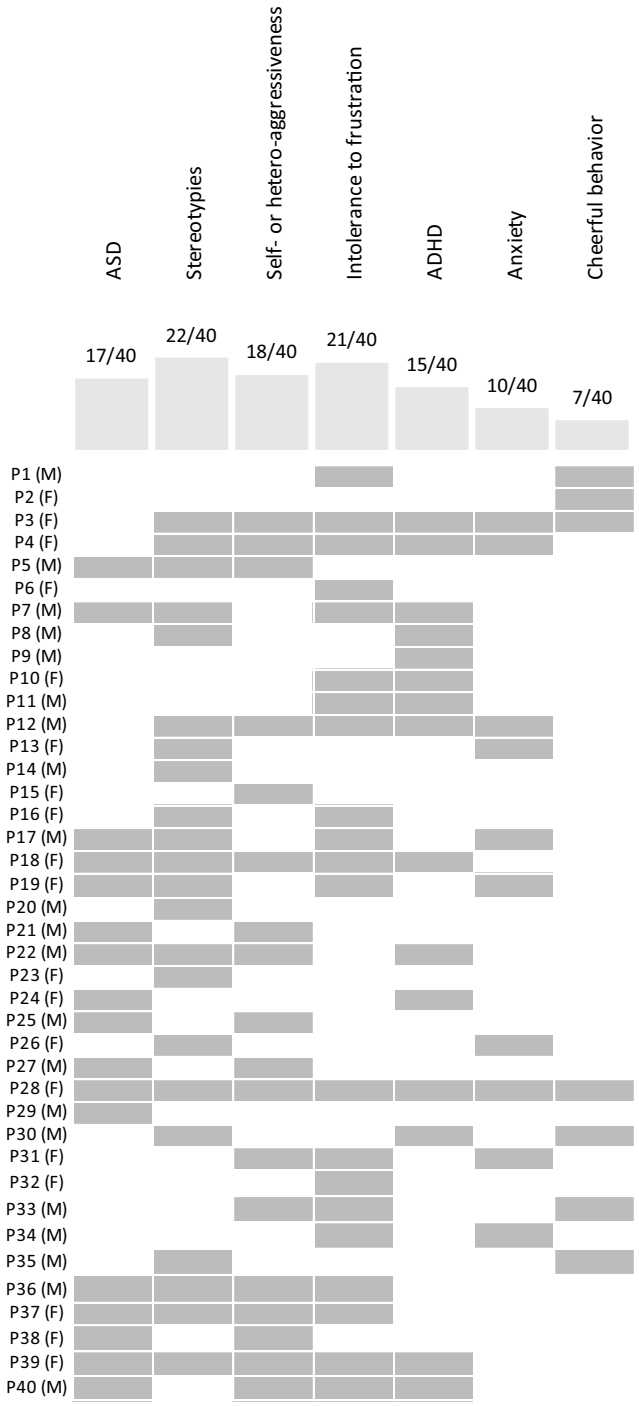

Fig. 1 Behavioral disorders in 40 individuals with *MYT1L*-related syndrome. Each patient is described in one line, according to six behavioral traits. Gray rectangles correspond to the presence of the phenotypic trait in the patient

in 18% (7/40) of the neonates. Seven patients (18%) presented with failure to thrive during the neonatal period or childhood that sometimes required early nutritional support through food fortification, nasogastric tube or even placement of a gastrostomy tube in one patient. In addition, intermittent vomiting, restrictive diet or dysphagia were noticed.

Most patients were overweight (23%) or obese (35%). The median age at onset of excessive weight gain, evaluated by clinicians in obese or overweight patients was 3.5 years. We plotted body mass index (BMI) curves (Fig. 2) for patients

with at least 3 height and weight data points (13 male and 14 female patients). While the females' charts appeared rather homogeneous in the ranges of overweight and obesity, the males' curves tended to show a bimodal distribution, with obese patients more clearly distinguished from those with normal weight. Strict and sustainable diet but also food intake control with parental supervision seemed effective in managing BMI in a few patients (for example P1 and P12, and also P40 regarding medical reports, not shown on Fig. 2). Eating behavior disorders were observed in 45% (18/40) of all patients and in 68% (16/23) of overweight/obese patients. Hyperphagia was frequently found and sometimes associated with tachyphagia and persistent absence of satiety.

Dysmorphic features

Various dysmorphic facial features were reported in 67% of participants in our series (26/39) (Fig. 3). We established a representative mask of the facial gestalt using the Face-2gene algorithm (Fig. 3). This *MYT1L* mask recapitulated the most frequent features observed in the patients with pathogenic *MYT1L* variants, including almond-shaped eyes with enophthalmos, a bulbous nose with slightly anteverted nostrils, full and sagging cheeks, a marked cupid's bow of the upper lip and thick and/or attached lobes for some patients.

Other symptoms

Ophthalmological disorders were noticed in 30% patients (12/40). Refractive errors were the most prevalent (72%), all identified in patients over 2 years of age, with five patients presenting with hyperopia, four patients having associated or isolated astigmatism and one patient having myopia. Five patients had strabismus of which two underwent surgery and two children had oculomotor apraxia. One patient had nystagmus.

Four patients presented with diverse endocrinologic abnormalities: Hashimoto's thyroiditis (P13), pituitary stem abnormalities with low prolactin (P7), hypogonadism (P27) and episodes of hypo- and hyperglycemia (P15). Hyperlipidemia was found in one child (P7). One patient had a micropenis and three others required surgery for uni- or bilateral cryptorchidism.

Sleep disorders were reported in 33% patients (13/40) and included difficulties with falling asleep, nocturnal

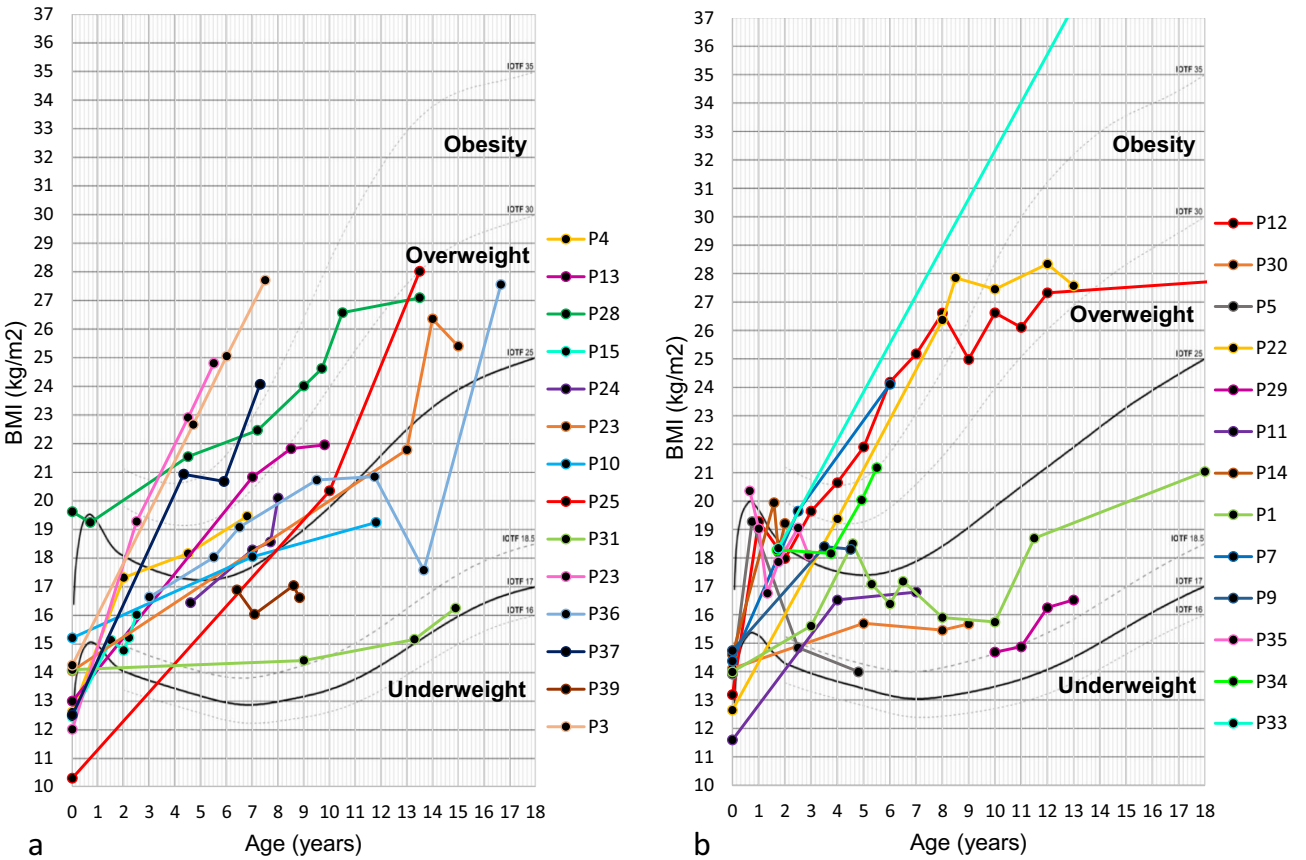

Fig. 2 Body mass index of individuals from birth to 18 years old (kg/m^2). **a** Female curves **b** Male curves

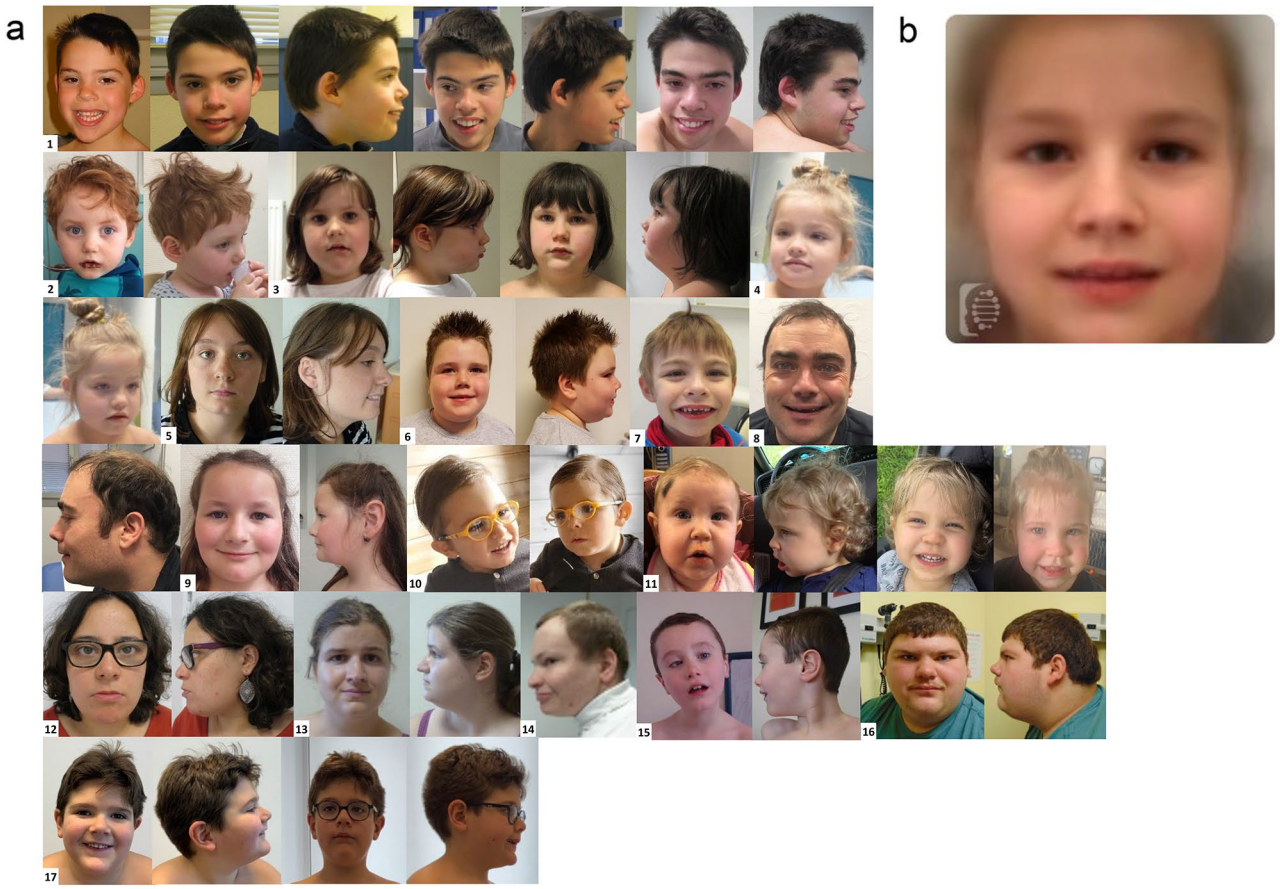

Fig. 3 Dysmorphic features in *MYT1L*-related disorder. **a** Photographs of 17 individuals with *MYT1L*-related syndrome from our cohort. (1) patient 1 frontal at age 6; frontal and profile at age 10; frontal and profile at age 14; frontal and profile at age 17; (2) patient 2 frontal and profile at age 2; (3) patient 3 frontal and profile at age 6; frontal and profile at age 7.5; (4) patient 4 frontal and ¾ at age 6.5; (5) patient 6 front and side at age 13; (6) patient 7 front and side at age 7; (7) patient 11 front at age 7.5; (8) patient 12 front and side at age 34; (9) patient 13 front and side at age 8; (10) patient 14 3/4 and side at age 4. 5 years; (11) patient 16 frontal at age 8 months; frontal and profile at age 18 months; frontal at age 28 months; (12) patient 19 frontal and profile at age 28 years; (13) patient 26 face and profile at age 30 years; (14) patient 27 profile at age 33 years; (15) patient 30 face and profile at age 9 years; (16) patient 33 face and profile at age 17 years; (17) patient 40 face and profile at age 6; patient 40 face and profile at age 7 after 4 months of diet. **b** *MYT1L* mask from face2gene research program. A composite of 11 photographs of participants has been used for the elaboration of the mask

awakenings or night terrors. Sleep apnea was identified in two patients, one of whom was not overweight.

Rarer clinical features included musculoskeletal abnormalities (kyphosis or scoliosis, ligament hyperlaxity, sprains, sacralization of the L5 vertebra), dermatologic features (hyper and hypopigmented areas and acanthosis nigricans in P28 and supracentimeter hypopigmented macules with jagged contours in P40), and visceral abnormalities (inguinal hernia in P12 and diaphragmatic hernia complicated by severe pulmonary arterial hypertension in P29).

Molecular characteristics and genotype–phenotype correlations

Likely pathogenic and pathogenic *MYT1L* variants from this study are represented in Fig. 4 and Supplementary Table 4. The distribution of LP/P missense variants in our cohort showed a high degree of clustering ($p = 7 \times 10^{-8}$, permutation test) (Fig. 4). The 2–3-ZNF domains represent 7.4% of the coding sequence (88/1184 residues) and contain 79% of the missense variants of our cohort (11/14), indicating a significant enrichment ($p = 1.13 \times 10^{-10}$, binomial exact test within our data), as previously suggested (Blanchet et al. 2017; Al Tuwaijri and Alfadhel 2019).

Interestingly, we observed a mirror distribution of missense variants in the gnomAD V2.1 database, suggesting

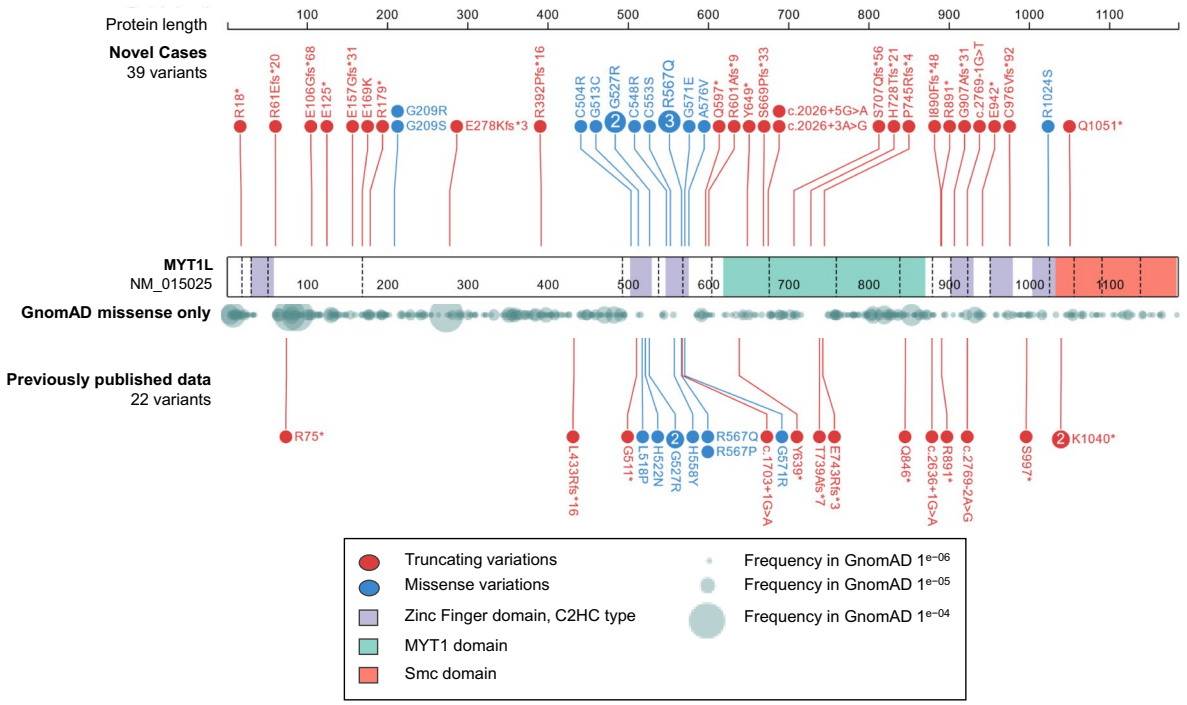

Fig. 4 Location of variants identified in this cohort and in previous published papers. Representation based on Protein Paint (https://proteinpaint.stjude.org/). Variants from the current cohort are represented on the upper panel. The variant resulting in the complete deletion of exon 9 (patient 38) is not shown on the Fig. 22 variants from previous published data are represented in the lower panel (Wang et al. 2016; Blanchet et al. 2017; Loid et al. 2018; Al Tuwaijri and Alfadhel 2019; Windheuser et al. 2020; Carvalho et al. 2021). GnomAD missense variants are displayed as controls from general population. Note the clustering of (likely) pathogenic variants in 2–3-ZNF domains both in literature and in this study, while these regions appear depleted in gnomAD

a negative selection for missense variants in these two domains (Fig. 4). This representation also shows other regions depleted for missense variants in gnomAD, including the positions around the three missense variants p.(Gly209Arg), p.(Gly209Ser) (outside ZNF domains) and p.(Arg1024Ser) (6th ZNF domain) that we report as likely pathogenic outside the 2nd and 3rd ZNF domains. Further studies are needed to explore the pathogenicity of missense variants in regions outside the 2nd and 3rd ZNF domains. Of note, in three unrelated patients we observed a recurrent variant, c.1700G > A, p.(Arg567Gln) variant in the 2nd ZNF domain. Two patients presented distinct genomic variants leading to the same p.(Gly527Arg) substitution, and two other patients harbored a substitution of the same c.625 nucleotide, leading to distinct amino acid substitutions.

We sought for a genotype–phenotype correlation by comparing truncating variants and missense variants in the 2nd and 3rd ZNF domains. These two domains are known to play a key role in the interaction with the DNA targets (Mall et al. 2017; Romm et al. 2005; Manukyan et al. 2018). We compared the phenotypic data of the combined literature and current study cohort between patients with truncating variants ($n = 40$) and patients with missense variants in the 2–3-ZNF domains ($n = 19$). Forty-one clinical criteria were used for clinical comparison (Supplementary Fig. 1). This analysis showed no difference in trait frequency between the two groups, except for the criteria "behavioral disorder" ($p = 0.031$, Fisher's exact test) and "epilepsy" ($p = 0.047$, Fisher's exact test), but this difference was no longer significant after correction for multiple testing (Bonferroni correction on 41 tests) (Supplementary Table 5). We also compared the dynamics of weight gain between those two variants groups within our data, by using the BMI curves (Supplementary Fig. 2). The non-significant Age*type of variant interaction (test of coefficient nullity, beta (Missense vs Truncating) = − 0.24, SE = 0.29, $p = 0.4087$) indicates that the slope is not different between individuals carrying missense or truncating variants. Moreover, type of variant marginal effect was not significant either (beta (Missense vs Truncating) = -0.84, SE = 0.94, $p = 0.3822$ in the whole model, and beta (Missense vs Truncating) = − 1.2, SE = 0.83, $p = 0.1624$ after removing interaction from the model) indicating that BMI at birth was not different between groups. Altogether, patients with missense variants clustered in 2nd and 3rd ZNF domains were clinically indistinguishable from patients with truncating variants, indirectly suggesting that these variants also cause a loss

of *MYT1L* function, most probably through impaired DNA binding of the protein.

Discussion

Our study increases the total number of patients reported with LP/P SNV/indels in *MYT1L* to 62, and provides an updated and more accurate description of the condition. Figure 5 presents an overview of the clinical aspects (counts appear on Table 1). Our study confirmed the main features of *MYT1L* haploinsufficiency, namely developmental delay and language impairment (95% in both literature and our study), behavioral disorders (90 and 98%) including ASD (43% in both), ADHD (48% and 38%) and aggressiveness (38% and 45%), early onset overweight/obesity (59% and 58%), eating behavioral disorder including hyperphagia (48% and 45%), epilepsy (29% and 23%), and non-specific brain MRI abnormalities (31% and 28%). Sleep disorders were relatively frequent (28% in literature data vs. 33% in our study), with nocturnal awakenings and difficulties falling asleep. Non-specific and

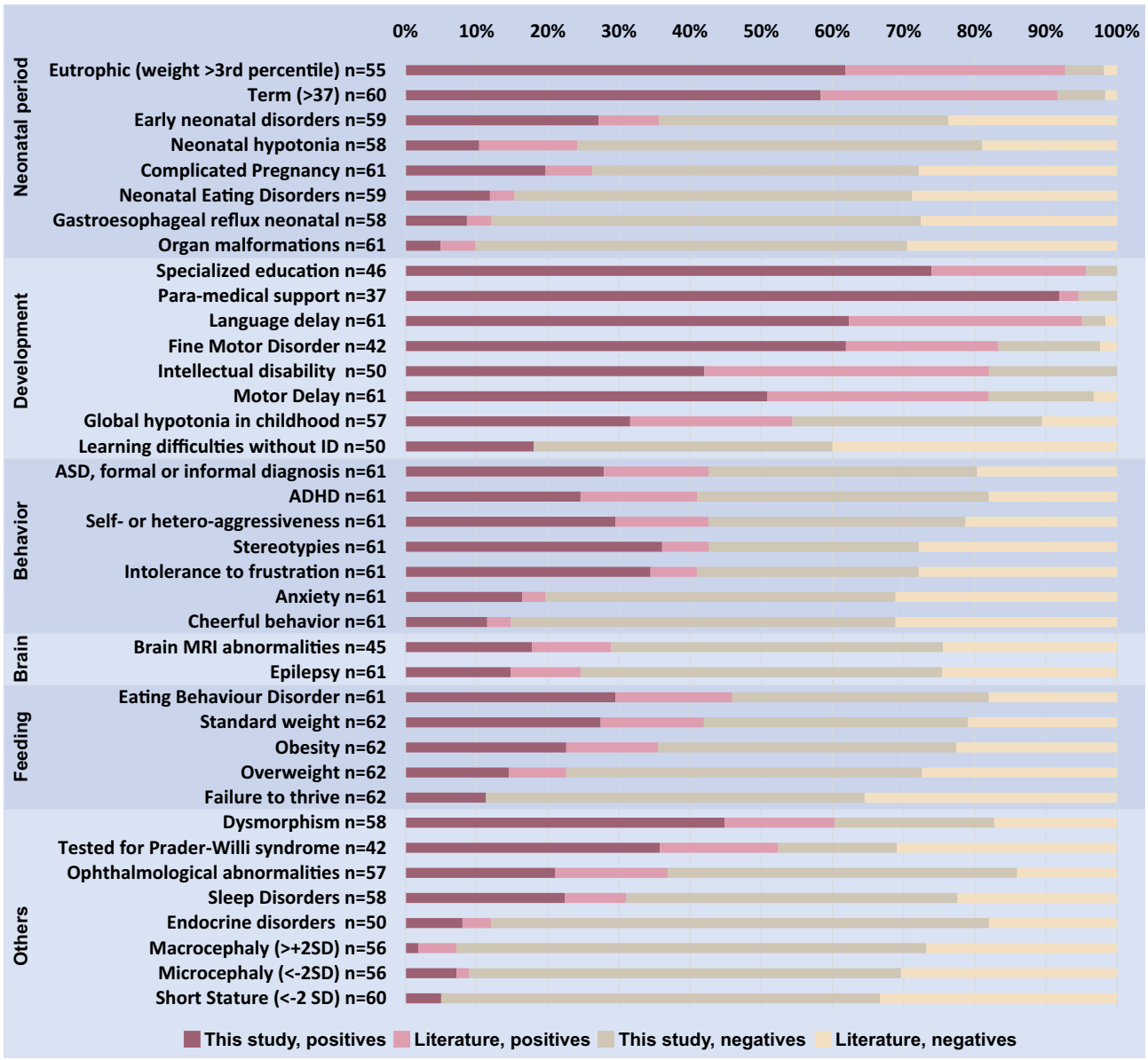

Fig. 5 Summary of key clinical signs identified in individuals with (likely) pathogenic *MYT1L* variants. Positive values among our patients are represented in dark pink; whereas, positive values among patients from literature are represented in light pink (Wang et al. 2016; Blanchet et al. 2017; Loid et al. 2018; Al Tuwaijri and Alfadhel 2019; Windheuser et al. 2020; Carvalho et al. 2021). In beige is represented the negative fraction for each of the clinical aspects

inconsistent craniofacial dysmorphic features had been reported by all previously published articles. Our data confirmed some common but inconsistent features 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. In addition to the main clinical features already well established, we highlight novel features. Patients may have difficulties in gaining weight in the neonatal or childhood period. These difficulties were associated in some patients with oral aversion, dysphagia, or vomiting and some required dietary support to increase caloric intake (nasogastric tube or hyper-caloric diet). These feeding difficulties were reminiscent of those in patients with Prader–Willi syndrome; however, all patients did not subsequently become obese or overweight. Of note, these seven patients harbored either truncating ($n=4$) or missense ($n=3$) variants, thus ruling out the hypothesis of an endo-phenotype caused by a specific category of variants.

We were able to specify the age of rapid weight gain in patients who were overweight or obese (median 3.5 years), suggesting early-onset obesity in *MYT1L*-associated disorder. We observed that some patients benefited from food restriction, with normalization of their weight curves after strict food monitoring by the families (P1 and P12, and also P40 regarding medical reports, not shown on Fig. 2). These results underscore the importance of global and multidisciplinary care with control of the patient's environment. It involves the establishment of a strict dietary framework, the limitation of access to food, and the ritualization of food intake and the practice of adapted, supported, and supervised physical activity (Poitou et al. 2020). However, in our study 43% of individuals were reported with a normal weight (BMI 18.5–25 kg/m2) according to the curves of the French Pediatrics Association (AFPA), which was comparable to the 41st % found in the literature. The role of *MYT1L* in hyperphagic obesity is not yet clearly understood in humans; Blanchet et al. (2017) recognized *MYT1L* to be involved in the leptin-melanocortin-SIM1 pathway downstream of SIM1-ARNT2 and demonstrated that in turn, *MYT1L* regulates oxytocin (OXT) expression in the hypothalamus. OXT is known to be involved in both autism and obesity pathogenesis (Francis et al. 2014). Interestingly, the loss of *MYT1L* function in zebrafish interferes with the development of the neuroendocrine hypothalamus and results in a loss of OXT expression in the hypothalamus (Blanchet et al. 2017). Intranasal OXT is currently under study in Prader-Willi syndrome (PWS), as patients have an OXT deficiency. Results in clinical trials in this population seem encouraging, suggesting that OXT may be a safe and effective treatment improving socialization, anxiety, repetitive behaviors and reducing food intake (Miller et al. 2017). Further studies are needed to investigate if OXT could also be a potential therapeutic target in *MYT1L*-associated neurodevelopmental disorder.

Our data also allowed us to refine the cognitive and neuropsychiatric phenotype. While ID was previously considered as consistent (Blanchet et al. 2017; Windheuser et al. 2020), we report nine patients without ID according to the observations of the referring physicians, leading to a prevalence of ID of only 70% in our cohort. However, despite the absence of ID, it should be noted that all patients had learning difficulties, of varying severity, but mostly severe. Some neuropsychological aspects stood out with the presence of a complex learning disorder associated with dysphasia, dyspraxia, dyscalculia, dysgraphia and attention deficit disorder. As a limitation of this study, standardized evaluation of intelligence, adaptive skills, and psychiatric disorders have not been performed for each individual, limiting the degree to which prevalence and severity of these traits can be assessed. Data from a larger number of patients with diagnoses evaluated in a standardized way will be needed to refine the neuropsychological profile of these individuals. Children with impulsivity or aggressivity had ID of varying severity, highlighting the fact that the presence of these behaviors cannot be entirely attributed to difficulties in verbal expression or understanding. In addition, we wondered if individuals with behavioral disorder and/or ID were more likely to be overweight or obese. We did not observe an association between these two variables (OR = 1 [0.12–6.65], p value = 1 (Fisher's exact test). Unexpectedly, despite the frequency of angry or frustrated behavior, 18% (7/40) of the additional patients we report here were also described as presenting a happy demeanor, although this phenotype was not further detailed (Rio et al. 2013; Doco-Fenzy et al. 2014; De Rocker et al. 2015; Windheuser et al. 2020). It had been suggested that macrocephaly, microcephaly and short stature might be over-represented among individuals with *MYT1L* variants compared to patients with larger microdeletions (Windheuser et al. 2020; Carvalho et al. 2021). While we found similar proportions of patients with microcephaly in our study compared to our review of the literature (6% in published data vs 11% in this study, regarding the criteria for microcephaly), we found a lower prevalence of macrocephaly (17% in published data vs 3% in our study) and therefore it is unclear if macrocephaly is indeed enriched in patients with *MYT1L* LP/P variants, as it had been proposed by other authors. We also identified fewer patients with short stature in our study than previously reported (8% (3/40) in our study as compared to 20.5% (9/44) reported by Windheuser et al. (2020)), possibly explained by different data collection methods.

We analyzed the mutational landscape in *MYT1L*, which confirmed that besides large deletions, the majority of SNV/indels consisted of either truncating variants predicted to lead to nonsense-mediated decay (NMD) or missense

variants mostly located in the 2nd and 3rd ZNF domains. We showed no phenotypic differences between patients harboring these two types of variants. We also described three patients with an indistinguishable phenotype, who carried de novo missense mutations outside the two main ZNF domains. Of note, two of these patients (P30 and P31) had a different substitution of the same nucleotide (G nucleotide at position 625) but leading to two different missense substitutions (respectively, p.(Gly209Arg) and p.(Gly209Ser)). The pathogenic mechanisms by which these variants likely lead to a loss of *MYT1L* function remain to be elucidated.

In conclusion, this international collaborative study increases the number of published patients with LP/P SNV/indels to 62 individuals, strongly supporting some well-known clinical features such as developmental delay, the presence of an ID of varying severity, ASD, hyperphagia, epilepsy, and also highlighting additional less frequent features associated with *MYT1L* mutations. We broaden the phenotype by reporting the first patients without ID and the first patients with failure to thrive and feeding difficulties. We specify the characteristics of the inconsistent craniofacial dysmorphisms. We identify no strong genotype–phenotype relationships, supporting the hypothesis that missense variants likely lead to a loss of *MYT1L* function. This case series further defines the clinical phenotype and the associated molecular alterations of this rare disease, with the objective of a better management of patients in their daily life, especially in terms of nutritional and neuropsychological care.

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Author contributions Dr Coursimault Juliette, Dr Lecoquierre François and Dr Gaël Nicolas contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr Juliette Coursimault and Dr François Lecoquierre. The first draft of the manuscript was written by Dr Juliette Coursimault and Dr Gaël Nicolas, Dr François Lecoquierre and Dr Anne-Marie Guerrot performed critical revision of the manuscript. All authors contributed to data acquisition. All authors read and approved the final manuscript.

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Availability of data and material De-identified clinical information tables are available upon request.

Code availability N/A

Declarations

Conflicts of interest FMZ, FZ, AS, SL and MMM are employees of GeneDx, Inc.

Ethical approval This retrospective study was approved by the Institutional Review Board of the Rouen University Hospital (CERDE, Comité d'Ethique pour la Recherche sur Données Existantes et Hors Loi Jardé, Rouen, France) (notification n°69–2020).

Consent to participate Informed consent was obtained from all participants included in the study.

Consent for publication Patients' guardians signed informed consent regarding publishing their data and photographs.

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