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ORIGINAL ARTICLE

MED13L-related intellectual disability: involvement of missense variants and delineation of the phenotype

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Abstract

Molecular anomalies in *MED13L*, leading to haploinsufficiency, have been reported in patients with moderate to severe intellectual disability (ID) and distinct facial features, with or without congenital heart defects. Phenotype of the patients was referred to "*MED13L* haploinsufficiency syndrome." Missense variants in *MED13L* were already previously described to cause the *MED13L*-related syndrome, but only in a limited number of patients. Here we report 36 patients with *MED13L* molecular anomaly, recruited through an international collaboration between centers of expertise for developmental anomalies. All patients presented with intellectual disability and severe language impairment. Hypotonia, ataxia, and recognizable facial gestalt were frequent findings, but not congenital heart defects. We identified seven de novo missense variations, in addition to protein-truncating variants and intragenic deletions. Missense variants clustered in two mutation hot-spots, i.e., exons 15–17 and 25–31. We found that patients carrying missense mutations had more frequently epilepsy and showed a more severe phenotype. This study ascertains missense variations in *MED13L* as a cause for *MED13L*-related intellectual disability and improves the clinical delineation of the condition.

Keywords *MED13L* · Intellectual disability · Mediator complex · Cardiopathy

Introduction

Mediator is a large coregulator complex conserved from yeast to humans. The complex has emerged as a master coordinator of cell lineage determination, integrating signaling from various transcription factors, epigenetic regulators and non-coding RNAs [1]. In response to various stimuli, mediator undergoes conformational changes and creates a DNA loop between activated enhancer elements and promoter, notably through interactions with cohesins [1]. Mediator physically bridges transcription factors bound at enhancer elements with the RNA polymerase II transcription machinery at core promoter regions [1]. Mediator is organized into four modules, i.e., the tail-, the middle-, the head-, and the CDK8-kinase module [2]. In vertebrates, the latter module is composed of CCNT1 and three additional proteins: CDK8, MED12, and MED13; or their respective paralogs: CDK19, MED12L, and MED13L [3]. Disease-causing variations have been identified in genes encoding the CDK8-module proteins. *MED12* variants cause syndromic intellectual disabilities (ID), namely Opitz-Kaveggia syndrome

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(MIM #305450), Lujan-Fryns syndrome (MIM #309520), and Ohdo syndrome (MIM #300895) [4]. *CDK19* interruption by a translocation breakpoint has been found to cause moderate ID with microcephaly and retinal folds in a patient [5]. Recently, *MED13L* haploinsufficiency have been identified in patients with moderate to severe ID, hypotonia, and distinctive facial gestalt (OMIM #616789) [6–10]. The recognizable syndrome was delineated by Asadollahi et al. [7] and broadened by further reports [6, 8, 10–15]. The gene is located on chromosome 12q24.21 and encodes MED13L (*alias* TRAP240L), expressed in heart and brain tissues [9]. Originally, the interruption of *MED13L* by a translocation breakpoint was identified in a patient with dextro-loop transposition of the great arteries (dTGA- MIM #608808) and intellectual disability (ID). Given that association, a cohort of 97 individuals with isolated dTGA was screened for *MED13L* sequence variations. Rare heterozygous missense variants were identified in four patients [9]. Familial segregation was not available for three variants and showed that the remaining variant was inherited from a healthy parent [9]. Updated annotations of the four variations showed that the variant c.2056A>C was reported 472 times in GnomAD database (http://gnomad.broadinstitute.org/). Variants c.752A>G and c.6068A>G were reported in GnomAD database once and the variant c.5615G>A was reported once in 1000G database (http://www.internationalgenome.org/). Therefore, clinical relevance of these variants remains unclear. It was hypothesized that missense variants were associated with congenital heart defects (CHDs), particularly dTGA, without intellectual disability [10].

To date, 33 additional patients with a *MED13L* variants or intragenic deletion were reported [6–8, 10, 12, 13, 15–22]. The DDD studies identified at least 19 patients with a *MED13L* variant, highlighting *MED13L* as one of the most common ID-causing gene [14, 23]. Variants were either identified by targeted sequencing, indicating that the condition could be suspected prior to the molecular analysis, or by exome sequencing [12]. Strikingly, no further dTGA was found and all patients presented with ID, characteristic facial gestalt, and less commonly aspecific CHD in 6/25 cases (patent foramen ovale, Fallot tetralogy, pulmonary atresia). To our knowledge, seven missense variants were identified in 11 patients, but the lack of precise clinical data in most of them precluded clarification of their clinical relevance or possible genotype-phenotype correlation [8, 13, 14, 17]. Here, we report on 36 patients with *MED13L* variations affecting its function, including seven missense variants in nine patients. We aim to better delineate the phenotype and discuss possible genotype-phenotype correlation.

Subjects and methods

Patients

Thirty-six patients from 35 families were recruited through an international collaboration between centers of expertise for developmental anomalies. All patients were clinically examined by a clinical geneticist. Two patients have been published previously, but more detailed information was reported here: P7 (ref. [19]) and P8 (ref. [18]). Informed consents were obtained for genetic tests, data sharing, and publication of patients' photographs.

Genetic analyses

Molecular investigations were performed in different diagnostic laboratories according to their routine procedure regarding testing in patients affected with ID. *MED13L* intragenic deletions were identified by array-CGH. *MED13L* sequence variants were identified by either next generation sequencing of custom gene panels designed for ID (P5, P6, P7, P8, P9, P10, P11, P23, P25, P26, P27, and P31) [19, 24] or by whole exome sequencing for the other patients. Missense variations were evaluated using the Alamut interface (Interactive Biosoftware, Rouen, France). Pathogenicity scores were predicted in silico with SIFT (http://sift.jcvi.org), PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/), and MutationTaster (http://www.mutationtaster.org/) softwares. All coordinates are provided for NM_015335.4 transcript in hg19 (genome build: GRCh37) and NP_056150.1 protein. Variant data have been submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/).

Results

MED13L molecular anomalies

MED13L intragenic deletions, ranging in size from 47 to 200 kb, were identified in five patients (P1, P2, P3, P4, and P24) (Fig. 1 and Table 1). When available, parental segregation showed that these occurred de novo. We identified a *MED13L* sequence variants in 31 patients from 30 families. In one family, recurrence in two sibs (P12 and P13) was observed, presumptively due to parental germinal mosaicism. Protein-truncating variants were identified in 27 patients and were distributed all over the gene (Fig. 1a). One protein-truncating variant, c.1708_1709del, was identified in two unrelated patients (P7-P15). Four variants were predicted to affect splicing (c.5588 + 1G>A - c.1009 + 1G>C and c.2345-3C>G and c.6225 + 1G>A). Variant c.1009 + 1G>C was identified in two unrelated patients (P25-P30). Seven likely

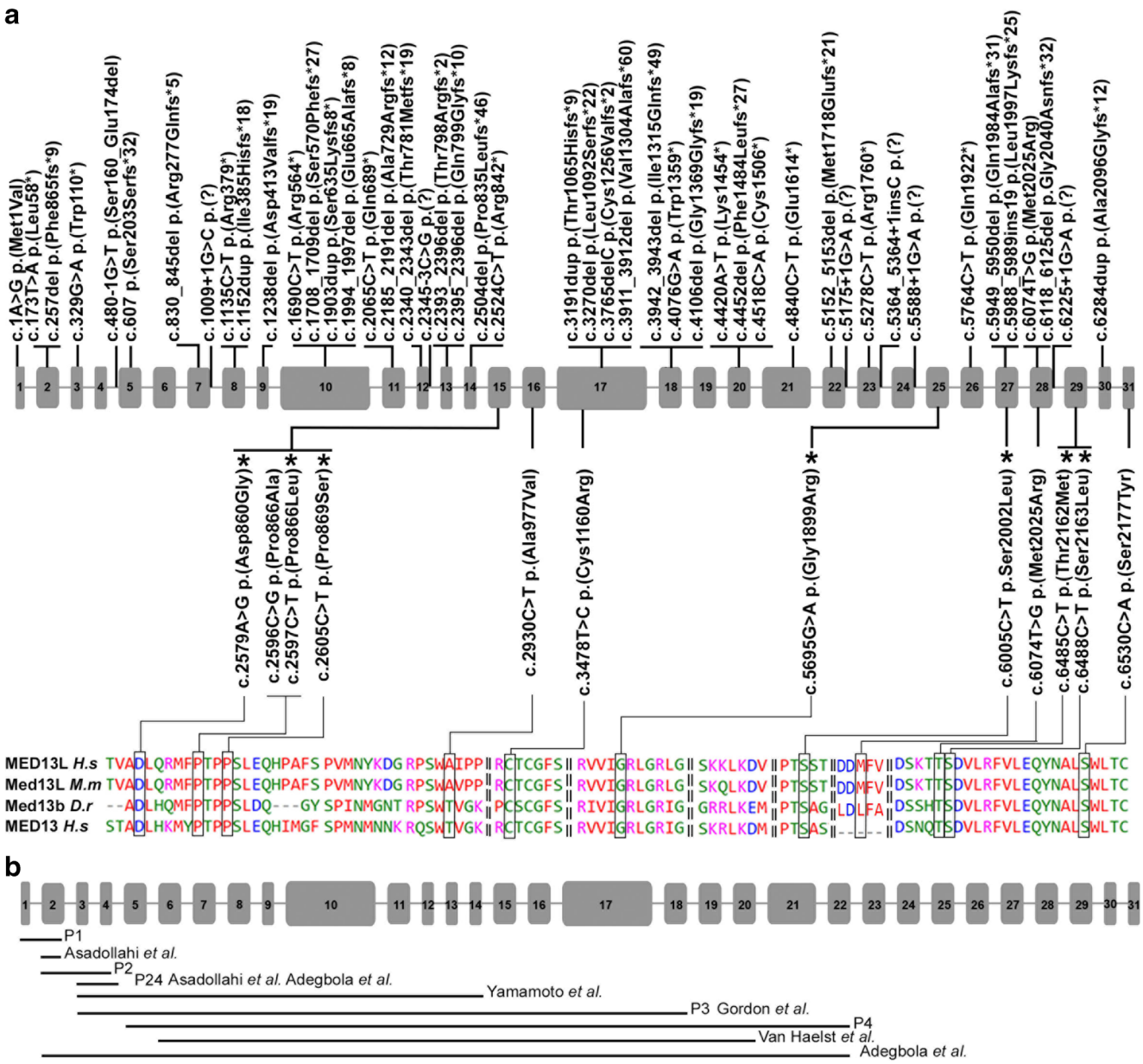

Fig. 1 **a** Summary of *MED13L* variants reported in the literature and in our cohort. Truncating variants are represented above the gene and missense variants under the gene. Asterisks indicate recurrent missense variants. Inter-species conservation of *MED13L* missense variations identified in the literature and in our series is shown. H.s, *Homo sapiens*; M.m, *Mus musculus*; D.r, *Danio rerio*. **b** Schematic representation of *MED13L* and location of intragenic deletions reported in our cohort (P1-P2-P3-P4 and P24) and in the literature, indicated by horizontal bars

pathogenic heterozygous missense variants were identified in nine patients (P14, P20, P21, P22, P23 P28, P32, P33, P35): c.2597C>T p.(Pro866Leu); c.2605C>T p.(Pro869Ser); c.2930C>T p.(Ala977Val); c.6005C>T p.(Ser2002Leu) c.6485C>T p.(Thr2162Met); c.6488C>T p.(Ser2163Leu) c.6530C>A p.(Ser2177Tyr) and were absent from GnomAD and ExAC database in well-covered regions. Both missense variants c.2605C>T p.(Pro869Ser) and c.6488C>T p.(Ser2163Leu) were identified in two unrelated patients, respectively in P28-P35 and P21-P23. Patient P20-P14 and P33 carried respectively the previously reported variants c.2597C>T p.(Pro866Leu), c.6005C>T p.(Ser2002Leu), and c.6485C>T p.(Tr2162Met)[14]. All missense variations were predicted to be "probably damaging" for PolyPhen2 (score > 0.98) and deleterious" for SIFT (score < 0.03). The seven missense variants were predicted to induce substitutions involving Pro866, Pro869, Ala977, Ser2002, Thr2162, Ser2163, and Ser2177 residues, which are highly conserved across vertebrates (PhyloP score 5.69 to 6.18—Fig. 1a). Except for Ala977, which presented a PhyloP score of 6.18, residues involved in these substitutions are also conserved in MED13, the MED13L paralog (Fig. 1).

Table 1 Clinical and molecular data of the 36 patients harboring likely pathogenic *MED13L* variants and comparison with the literature

Patient	1	2	3	4	5	6	7	8	9	10
Gender	F	M	M	M	M	F	M	M	M	M
Age at first examination (years)	2	3.8	9	9	11	4	4	10	13	4.75
DD/ID	+	+	+	+	+ (moderate)	+ (severe)	+ (moderate)	+ (moderate)	+ (moderate)	+ (severe)
Speech delay	+	+	+	+	+	+	+	+	+	+
Speech features	abs.	few words	NA	few words	few words	abs.	abs.	few words	NA	few words
Motor delay	+	+	+	+	+	+	+	+	+	+
Walk (months)	23	29	25	36	23	17	24	22	30	25
Hypotonia	+	–	+	+	+	+	–	+	+	+
Ataxia	–	–	–	+ (dysarthria)	–	–	–	+ (dysarthria)	+	+
Seizures	–	–	–	–	–	–	–	–	–	–
Autistic features	–	+	NA	+	–	+	–	+	–	–
Behavioral troubles	–	–	–	+	–	+	–	+	+	+
MRI	NA	NA	NA	Moderate VM	NA	WM hypersignal	Normal	Normal	Normal	Normal
Upslanting palpebral fissures	+	–	–	–	NA	–	–	–	+	–
Bulbous nasal tip	+	+	+	+	NA	+	+	+	+	+
Cupid-bow upper lip	–	+	+	+	NA	–	+	+	+	+
Hypotonic open-mouth	+	+	+	+	NA	+	+	+	–	+
Thin vermillon border	–	+	+	+	NA	–	–	–	–	+
Deep philtrum	+	NA	+	+	NA	–	+	–	+	+
CHD	+ (patent foramen ovale)	NA	–	NA	NA	–	–	–	–	–
Miscellaneous	Duplicated thumb	II-III toes syndactyly, cryptorchidism		Micropenis		Hirsutism	Adducted thumb	Syndactyly, coloboma	Large incisors	Club feet
MED13L molecular anomalies	exon 1–2 deletion	exon 2 to 4 deletion	exon 3 to 18 deletion	exon 5 to 22 deletion	c.173 T > A p.(Leu58*)	c.5278C > T p.(Arg1760*)	c.1708_1709del p.(Ser570Phefs*27)	c.6118_6125del p.(Gly2040Asnfs*32)	c.1152dup p.(Ile385fs*18)	c.4452del p.(Phe1484Leufs*27)
Parental segregation	NA	de novo	de novo	de novo	de novo	de novo	de novo	de novo	NA	de novo

Patient	11	12	13	14	15	16	17	18	19	20
Gender	F	M	F	F	M	M	F	M	M	M
Age at first examination (years)	2.75	9	19	4.25	7	8.5	34	31	10	15
DD/ID	+ (severe)	+	+	+	+ (moderate)	+ (severe)	+ (moderate)	+ (moderate)	+ (moderate)	+ (severe)
Speech delay	+	+	+	+	+	+	+	+	+	+
Speech features	abs. (disyllabic)	few words	NA	few words	NA	abs.	few words	few words	few sentences	abs.
Motor delay	+	+	+	+	+	+	+	+	+	+
Walk (months)	30	30	30	26	NA	24	20	NA	41	abs.
Hypotonia	+	+	–	–	+	+	+	NA	+	+
Ataxia	–	+ (dysarthria)	+	–	+	–	+	–	–	+
Seizures	–	–	–	–	NR	+	–	–	–	+
Autistic features	NA	NA	NA	–	NA	+	–	–	–	+
Behavioral troubles	–	NA	+	–	–	+	–	–	–	–
MRI	WM hypersignal	Labyrinthic malformations	Pituitaty adenoma	Normal	Subarachnoid spaces enlargement	Normal	NA	CC agenesis	Focal polymicrogyria	Normal
Upslanting palpebral fissures	+	–	–	–	–	–	–	+	–	NA

Table 1 (continued)

Patient	11	12	13	14	15	16	17	18	19	20
Bulbous nasal tip	+	+	+	–	+	–	+	+	+	+
Cupid-bow upper lip	+	–	–	–	NA	–	–	NA	+	–
Hypotonic open-mouth	+	+	+	+	NA	–	+	+	–	+
Thin vermillon border	–	–	–	+	+	+	–	–	–	–
Deep philtrum	+	–	–	–	NA	+	–	NA	+	–
CHD	–	–	–	–	NA	–	–	–	–	–
Miscellaneous	CBH syndrome	Obsesity, cryptorchidism, pyramidal syndrome	Obsesity, pyramidal syndrome	Kidney cysts	Posterior cleft palate	Strabismus, cryptorchidism	Hypopallesthesia	Hirsutism, strabis-mus	Robin sequence, 3–4-5 Toe clinodactyly, severe scoliosis	Nystagmus, craniosynos-tosis
MED13L molecular anomalies	c.5152_5153del p.(Met1718Glufs*21)	c.5588 + 1G > A p.(?)	c.5588 + 1G > A p.(?)	c.6485C > T p.(Thr2162Met)	c.1708_1709del p.(Ser570Phefs*27)	c.6284dup p.(Ala2096Glyfs*12)	c.830_845del p.(Arg277Gln*5)	c.2065C > T p.(Gln689*)	c.3942_3943del p.(Ile1315Glnfs*49)	c.2597C > T p.(Pro866Leu)
Parental segregation	de novo	de novo	de novo	de novo	de novo	de novo	de novo	NA	de novo	de novo

Patient	21	22	23	24	25	26	27	28	29	30
Gender	F	F	F	F	F	M	M	F	M	F
Age at first examination (years)	9	8	12	1.6	0.7	2.5	2.7	12	2	39
DD/ID	+ (severe)	+	+ (severe)	+	+	+	+	+	+	+
Speech delay	+	+	+	+	NA	+	+	+	+	+
Speech features	abs.	few words	few words	few words	NA	few words	NA	abs.	few words	few sentences
Motor delay	+	+	+	+	+	+	+	+	+	+
Walk (months)	30	25	26	Not acquired yet	NA	23	abs.	abs.	NA	20
Hypotonia	+	–	+	+	+	+	+	–	+	–
Ataxia	–	–	+	–	NA	+ (dysarthria)	NA	–	–	+
Seizures	+	–	–	–	–	–	–	+	–	–
Autistic features	+	+	–	–	NA	–	–	NA	–	–
Behavioral troubles	–	+	–	–	–	+	+	NA	–	+
MRI	Normal	Focal cortical dysplasia	NA	NA	NA	Normal	NA	CCH- Hypomyelination	NA	Normal
Upslanting palpebral fissures	–	–	+	–	–	+	–	+	+	+
Bulbous nasal tip	+	–	+	+	–	–	–	+	+	+
Cupid-bow upper lip	–	–	+	+	+	+	–	+	+	+
Hypotonic open-mouth	+	–	+	+	+	+	–	+	+	+
Thin vermillon border	–	–	+	–	+	+	+	+	+	+
Deep philtrum	–	–	+	–	+	+	–	+	+	+
CHD	–	–	–	–	Pulmonary vavular stenosis	–	–	–	–	–
Miscellaneous			Vertebral artery occlusion	Bilateral talipes, umbilical hernia			Bilateral talipes	IUGR clynodactyly- double ureter-CoAo	5 Toe clinodactyly	
MED13L	c.6488C > T	c.2930C > T	c.6488C > T	exon 3 to 4 deletion	c.1009 + 1G > C	c.2340_2343del		c.2605C > T	c.1903dupA	c.1009 + 1G > C

Table 1 (continued)

Patient	21	22	23	24	25	26	27	28	29	30
molecular anomalies	p.(Ser2163Leu)	p.(Ala977Val)	p.(Ser2163Leu)		p.(?)	p.(Thr781Metfs*19)	c.3911_3912del p.(Val1304Alafs*60)	p.(Pro869Ser)	p.(Ser635Lysfs8*)	p.(?)
Parental segregation	NA	de novo	de novo	de novo	de novo	de novo	NA	de novo	de novo	de novo

Patient	31	32	33	34	35	36	This study ($n = 36$)	Previous studies ($n = 30$)	Total ($n = 66$)
Gender	F	M	F	M	M	F			
Age at first examination (years)	4	5	9	17	24	3			
DD/ID	+	+	+	+	+	+	100% (36/36)	100% (30/30)	100% (66/66)
Speech delay	+	+	+	+	+	+	100% (36/36)	100% (30/30)	100% (66/66)
Speech features	few words	few words	abs.	few words	abs.	few words			
Motor delay	+	+	+	+	+	+	100% (36/36)	100% (19/19)	100% (55/55)
Walk (months)	NA	18	abs.	30	abs.	19			
Hypotonia	NA	+	+	+	+	–	77% (26/34)	62% (18/29)	68% (44/63)
Ataxia	–	+	NA	–	NA	+	34% (11/32)	32% (9/28)	33% (20/60)
Seizures	–	+	–	–	+	–	17% (6/35)	14% (4/28)	16% (10/63)
Autistic features	–	+		–	–	–	34% (10/29)	21% (6/29)	28% (16/58)
Behavioral troubles	–	+	–	–	–	–	31% (10/32)	32% (6/19)	31% (16/51)
MRI	Normal	NA	CCH-VM	Fine splenium	Diffuse cortical atrophy				
Upslanting palpebral fissures	NA	NA	+	+	–	–	34% (11/32)	62% (15/23)	47% (26/55)
Bulbous nasal tip	NA	–	+	+	+	+	82% (27/33)	74% (17/23)	79% (44/56)
Cupid-bow upper lip	NA	NA	–	+	+	–	58% (18/31)		
Hypotonic open-mouth	NA	NA	–	+	+	–	78% (25/32)	78% (14/18)	78% (39/50)
Thin vermillon border	NA	NA	+	–	+	+	52% (17/33)		
Deep philtrum	NA	NA	–	–	+	+	58% (18/31)		
CHD	NA	–	+ (patent foramen ovale)	–	–	NA	11% (3/27)	24% (6/25)	17% (9/52)
Miscellaneous	NA	Bilateral club foot	IUGR, growth retardation, colobomatous microphtalmia, bilateral talipes, ectopic anus	Assymetric face -assimetric microphtalmia	Feeding difficulties - hearing impairment- myopia	Feeding difficulties in infancy			
MED13L molecular anomalies	c.2345-3C > G p.(?)	c.6530C > A p.(Ser2177Tyr)	c.6005C > T p.(Ser2002Leu)	c.6225 + 1G > A p.(?)	c.2605C > T p.(Pro869Ser)	c.5764C > T p.(Gln1922*)			
Parental segregation	de novo	de novo	de novo	de novo	de novo	de novo			

abs., absent speech; *CC*, CoAo, coarctation of the aorta; Corpus Callosum; *CBH*, Claude Bernard-Horner; *CHD*, congenital heart disease; *DD*, developmental delay; *F*, female; *ID*, intellectual disability; *M*, male; *MRI*, magnetic resonance imaging; *NA*, non available; *VM*, VentriculoMegaly; WM, white matter; *IUGR*, intrauterin growth retardation

Fig. 2 Morphological features of a selection of patients. **a** Patients with protein-truncating variants. Core facial features comprises depressed nasal bridge, horizontal eyebrows, full cheeks, and large open mouth. Majority of patients show also cupid-bow upper lip, thin vermilion border, and deep philtrum. **b** Patients P20-P28 and P35 (at different age) show atypical facial gestalt with long down-slanting palpebral fissures and everted lower eyelids. **c** Some patients, notably in infancy have broad, stubby, and tapering fingers. Feet showed long halluces and sandal-gap deformity in some patients. **d** Photo enlargement of the palpebral features of patients P20-P28 and P35

Phenotypic findings

Patient with protein-truncating mutation

Protein-truncating variants were identified in 27 patients. No remarkable prenatal history was reported and birth parameters were normal for all individuals. Motor skills were delayed, median age for independent walking being 25 months (range from 17 to 41 months). One patient did not achieve walking but he was only 32-month-old. Speech was also severely impaired in most individuals, composed of few words (16/21–52%) or even absent (5/21–24%). All patients showed moderate to severe ID. Global hypotonia was observed in 20/25 (80%) patients. Ataxia was noticed in 9/25 patients (36%), consisting mainly in dynamic ataxia and dysarthria in four patients. We did not retrieve age at onset of the cerebellar signs, but mean age of the patients with ataxia was 12 years (ranging from 2 to 39 years). One patient presented with seizures (1/26–4%). Autistic features were noticed in 5/21 (24%) cases and behavioral troubles in 10/26 (39%), consisting in aggressive behavior when specified. Brain magnetic resonance (MRI) imaging showed various non-specific anomalies comprising ventriculomegaly, myelination defect, corpus callosum anomaly, or focal cortical dysplasia (Table 1). Majority of the patients shared common facial features with wide open mouth, protruding tongue (without macroglossia), full cheeks, bulbous nasal tip, and horizontal eyebrows. Some patients showed thin vermilion, deep philtrum, and cupid-bow upper lip (Fig. 2 and Table 1). Echocardiography revealed patent foramen ovale in two patients (P1) and pulmonary valvular stenosis in one patient (P25) (Supplemental Table 1).

Patient with missense variation

Missense variants were identified in nine patients. Intra-Uterine Growth Retardation (IUGR) was observed only in P33. Median

age for independent walking was also 25 months (range from 18 to 30 months), but 4/9 patients (44%) were not able to walk at the age of examination (P20-P28-P33-P35). The latter patients either did not achieve independent walking (P28-P33) or achieved independent walking and then lost ability to walk because of worsening of epilepsy (P20-P35). Speech was absent in 5/9 patients (56%) and composed of few words in 4/9 patients (44%). Global hypotonia was observed in 6/9 patients (67%). Ataxia was noticed in 3/7 patients (43%). Six patients presented with seizures 6/9 patients (67%), consisting in febrile seizure (P32), late onset infantile spasms (P20) and Lennox-Gastaut syndrome (P35). Abnormal brain magnetic resonance imaging (MRI) showed various non-specific anomalies in 4/7 patients (57%), comparable with these found in patients with protein-truncating variations (supplemental Table 1). We observed atypical facial features in three patients (P20-P28-P35). They showed long down-slanting palpebral fissures, with everted lower eyelids (Fig. 2d). Echocardiography revealed a patent foramen ovale in one patient (P33) (Table 1).

Discussion

Here we report on a cohort of 36 patients carrying *MED13L* anomalies, including two previously published cases, allowing a better delineation of the associated phenotype. All individuals had motor delay, speech delay, and moderate to severe ID. In most patients, language was limited to few words or was even absent. Patients showed various degrees of cerebellar dysfunction. Ataxia was observed in 11/32 patients, and was reported especially in the older cases (P9 –P10-P13-P15-P17-P20-P23-P32–P32-P36). Since this feature was under-reported in younger patients, we hypothesize that cerebellar involvement probably worsened with age. No patient showed cerebellar anomaly on brain MRI, but repeated imaging may be needed to explore possible progressive atrophy. MRI identified aspecific features comprising myelination defects, corpus callosum abnormalities, white matter anomalies, ventriculomegaly and focal cortical dysplasia. This study confirms that most patients show a recognizable facial gestalt, which could phenotypically overlap with deletion 1p36 microdeletion syndrome (OMIM# 607872) in some patients [12]. Core facial features comprise depressed nasal bridge, horizontal eyebrows, full cheeks, and large open mouth [7, 12]. More subtle features like cupid-bow upper lip, thin vermilion border, and deep philtrum can be observed. However, in a few patients, these core facial features were absent (P22-P27). We also noticed that non-recurrent facial features can be associated, especially in patients with a missense variant located in the exon 15 (P20-P28-P35) (Fig. 2b). In our cohort, patients were not suspected with the condition prior to genetic testing, but secondarily facial comparison allowed the description of common features. These data highlight the valuable role of clinical geneticists in the precision of the phenotype, a critical step to determine the pathogenicity of *MED13L*-variants.

We found only three patients with CHD, consisting in patent foramen ovale or pulmonary valvular stenosis but no complex CHD (Table 1). Patients carried respectively *MED13L* intragenic deletion, splice-site variant, and missense variant (P1-P25-P33), confirming that frequency of complex CHD is less than initially expected and is not correlated with *MED13L*-missense variants. Concerning patients reported by Muncke et al., showing dTGA and probably no developmental delay [9], it is unlikely that their variants affect the protein function. *MED13L* is located next to *TBX3* and *TBX5* genes. These genes respectively cause ulnar-mammary syndrome (OMIM#181450) and Holt-Oram syndrome (OMIM#142900), both conditions comprising CHD. Heart-specific enhancers have been identified within regulatory domains of both genes; however, they do not overlap with regions contacting MED13L [25]. Therefore, it is unlikely that *MED13L* variants could affect cis-regulatory elements controlling *TBX3* or *TBX5* expression during heart development. Involvement of *MED13L* in the dTGA of these patients remains to be explained.

We observed clinical variability, notably in patients who carried recurrent variations (P12-P13; P21-P23; P7-P15; P25-P30; P28-P35) (Table 1). As suggested by Asadollahi et al., we found that patients with missense variants were more prompt to develop epilepsy, compared to patients with protein-truncating variants (4/9 versus 1/26) [8]. Severe neurodevelopmental phenotype (absent speech in 5/9 versus 5/21—non ambulatory 4/9 versus 1/21) and malformations are also more frequent (Supplemental Table 1). More precisely, patients P20 and P35 lost the ability to walk consecutively to worsening of epilepsy. They needed gastrostomy tube feeding and P35 had hearing impairment and severe myopia. P33 showed a severe phenotype associating IUGR, absent speech, microcephaly, colobomatous microphthalmia, and never achieved sitting. Moreover, P20-P28 and P35 showed atypical facial features with long palpebral fissures and even everted lower eyelid in P20 and P35 (Fig. 2b). Based on these particular palpebral features, P20 was initially diagnosed with Kabuki syndrome (OMIM #147920). All these data are supported by clinical features from the 11 patients reported in the literature, carrying missense variants [8, 13, 14, 17]. Clinical details of the patients reported by the DDD study were retrieved from Decipher database (https://decipher.sanger.ac.uk/) and corresponded to patients' ID: #272205, #260542, #262717, #258131, #268019, #262545, #265953, and #323183. Among them, four patients had epilepsy, and two patients had IUGR and atypical features were also noted (craniosynostosis, microcephaly, major feeding difficulties, limb malformations). Since patients with missense mutation seem to have a more severe phenotype, we could hypothesize that they induce a dominant negative effect, contrarily to protein-truncating variants. We did not consider the patient reported by Mullegama

et al., who suffered from speech delay, ASD and Mediterranean fever. He carried *MED13L*, *DEAF1*, and *MEFV* variants [26]. Inheritance of the *MED13L* missense variant c.5282C>T p.(Prol1761Leu) could not be determined, since the patient was adopted. Polyphen2 and SIFT software predicted in silico that the variant was respectively benign and tolerated. There is no experimental evidence of the deleterious effect on the function of the protein. Thus, there was not enough evidence to consider the variant as the cause of the neurodevelopmental disorder of the patient.

The seven missense variants identified in this study, as well as the *MED13L*-missense variants previously reported in the literature, cluster in exons 15–17 and 25–31 (Fig. 1) [8, 13, 14, 17]. Both localizations constitute hot-spots of mutations. As expected, majority of missense variations are recurrent [8]. Previously reported variants c.2597C>T p.(Pro866Leu), c.6005C>T p.(Ser2002Leu), c.6485C>T p.(Thr2162Met) were identified in three patients [8, 13, 14, 17]. We identified four novel missense variants in six patients: variant c.2605C>T p.(Pro869Ser) was identified in two patients and as well as variant c.6488C>T p.(Ser2163Leu). Variants c.2930C>T p.(Ala977Val) and c.6530C>A p.(Ser2177Tyr) were not recurrent. One of the MED13/MED13L functions is to physically link the CDK8-module to the core Mediator complex, mainly by interacting with MED19 and CDK8 [27]. Dissociation of the CDK8-module components from the core Mediator is mediated by Mediator-bound MED13/MED13L ubiquitylation and degradation [28]. Both subunits can also relay information from temporal/spatial signals or transcription factors to the RNA polymerase II machinery, thus controlling the expression of specific genes, notably genes involved in Wnt, FGF, and Rb/E2F pathways [8]. Since all the residues involved in the substitutions are located in highly conserved across vertebrate regions and even conserved in MED13, we can assume that these residues are probably implicated in such mechanisms. Further studies are needed to unravel the deleterious mechanism induced by these molecular changes.

Conclusion

In this cohort of 36 patients with *MED13L*-related intellectual disability, we confirmed recognizable facial gestalt and intellectual involvement. We highlighted possible arising of progressive cerebellar signs. We did not confirm congenital heart defects as a major feature of the condition. Patients with missense variant are significantly more at risk to develop epilepsy and seemed to have a more severe phenotype, suggesting possible dominant negative effect of the missense variants. We observed clustering of missense variants in specific domains of the protein. Substitution involving the highly conserved across species residues Asp860, Pro866, Pro869, Gly1899, Ser2002, Thr2162, and Ser2163 were identified in at least two patients. Precise roles of these domains and specific residues remain to be determined to better understand molecular mechanisms underlying *MED13L*-related intellectual disability.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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