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Genotype-phenotype evaluation of *MED13L* defects in the light of a novel truncating and a recurrent missense mutation

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ABSTRACT

A decade after the designation of *MED13L* as a gene and its link to intellectual disability (ID) and dextro-looped transposition of great arteries in 2003, we previously described a recognizable syndrome due to *MED13L* haploinsufficiency. Subsequent reports of 22 further patients diagnosed by genome-wide testing further delineated the syndrome with expansion of the phenotypic spectrum and showed reduced penetrance for congenital heart defects. We now report two novel patients identified by whole exome sequencing, one with a *de novo MED13L* truncating mutation and the other with a *de novo* missense mutation. The first patient indicates some facial resemblance to Kleefstra syndrome as a novel differential diagnosis, and the second patient shows, for the first time, recurrence of a *MED13L* missense mutation (p.(Asp860Gly)). Notably, our *in silico* modelling predicted this missense mutation to decrease the stability of an alpha-helix and thereby affecting the MED13L secondary structure, while the majority of published missense mutations remain variants of uncertain significance. Review of the reported patients with *MED13L* haploinsufficiency indicates moderate to severe ID and facial anomalies in all patients, as well as severe speech delay and muscular hypotonia in the majority. Further common signs include abnormal MRI findings of myelination defects and abnormal corpus callosum, ataxia and coordination problems, autistic features, seizures/abnormal EEG, or congenital heart defects, present in about 20–50% of the patients. With reference to facial anomalies, the majority of patients were reported to show broad/prominent forehead, low set ears, bitemporal narrowing, upslanting palpebral fissures, depressed/flat nasal bridge, bulbous nose, and abnormal chin, but macroglossia and horizontal eyebrows were also observed in ~30%. The latter are especially important in the differential diagnosis of 1p36 deletion and Kleefstra syndromes, while the more common facial gestalt shows some resemblance to 22q11.2 deletion syndrome.

Despite the fact that *MED13L* was found to be one of the most common ID genes in the Deciphering Developmental Disorders Study, further detailed patient descriptions are needed to explore the full clinical spectrum, potential genotype-phenotype correlations, as well as the role of missense mutations and potential mutational hotspots along the gene.

1. Introduction

MED13L (Mediator complex subunit13-like) was established as a gene followed by the mapping of a translocation breakpoint on chromosome 12 in a patient with intellectual disability (ID) and dextro-looped transposition of great arteries (dTGA) (Muncke et al., 2003). They introduced the gene by completing the transcriptional unit of the previously nominated *KIAA1025* and named it

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PROSIT240, protein similar to thyroid hormone receptor–associated protein 240. Independently, in a Noonan-like patient, Musante et al. (2004), fine-mapped a translocation to the vicinity of the same gene which they further characterized by RT-PCR and 5-prime RACE of cDNA libraries and called *THRAP2*, thyroid hormone receptor–associated protein 2. Eventually, the PROSIT240/THRAP2 protein was shown to be a subunit of the Mediator complex and was designated as MED13L due to its homology with MED13 (Sato et al., 2004).

Though the Mediator complex is known to link DNA-binding transcription factors and RNA polymerase II for gene transcription (Sato et al., 2004), the explicit role of MED13L has not been completely understood.

Clinically, after the initial finding of a link between *MED13L* and ID/dTGA (Muncke et al., 2003) and report of a candidate homozygous missense mutation of *MED13L* in non-syndromic ID (Najmabadi et al., 2011), we previously described a recognizable *MED13L* haploinsufficiency syndrome as a possible neurocristopathy to be considered in the differential diagnosis of 22q11.2 deletion syndrome (Asadollahi et al., 2013). Subsequent reports of additional patients with *MED13L* loss-of-function (LOF) defects (Adegbola et al., 2015; Cafiero et al., 2015; Caro-Llopis et al., 2016; Codina-Sola et al., 2015; Hamdan et al., 2014; Redin et al., 2014; Utami et al., 2014; van Haelst et al., 2015; Yamamoto et al., 2017) have further illustrated the phenotypic spectrum of the syndrome (Tables 1 and 2), and functional studies by Utami et al. (2014), have indeed evidenced defective neural crest cells in the pathogenesis of the *MED13L* haploinsufficiency syndrome.

Here, we describe two new cases, and highlight the common features and phenotypic spectrum of patients harbouring *MED13L* LOF aberrations, as well as the role of missense mutations. Furthermore, we discuss what is known about the biological role of MED13L as a kinase module subunit of the Mediator complex in performing general and specific functions.

2. Ethics

Genetic testing in this study was either performed on a diagnostic basis with subsequent consent for publication or as part of a research study approved by the ethics commission of the canton of Zurich. Written informed consent including consent for whole exome sequencing as well as for publication of clinical information and photographs was obtained from the parents who also consented on behalf of their children.

3. Description of new patients

3.1. Patient 1

Patient 1 (Fig. 1A–H), a 14-year-old girl, is the second child of healthy, non-consanguineous Swiss parents aged 32 (mother) and 35 (father) at the time of conception. Her older sister is healthy. She was born after an uneventful pregnancy at term with a weight of 3500 g (50th centile). Club feet, pes adductus and a large protruding tongue were noted in the neonate. At the age of 1.5 years the latter in addition to facial dysmorphism such as upslanting palpebral fissures, midfacial retraction, rather small ears and tapering fingers led to the suspicion of mosaic trisomy 21, which was excluded by conventional karyotyping. Cardiological investigations revealed no anomalies. The neonatal period was complicated by muscular hypotonia, opisthotonus, feeding difficulties, and failure to thrive. The latter continued and were attributed to difficulties to swallow and gastroesophageal reflux disease. Motor and speech development were delayed with a sitting age of 11 months, walking age of 3 years and first words at 3 years. At the age of about 8 years, she developed absence seizures with eyelid myoclonia which were successfully treated with Orfiril. Surgical treatment of her feet deformities were performed at the age of about 9 years.

At the age of 11 years and 7 months, growth parameters were within the normal range (weight 39 kg (50th centile), height 139.8 cm (10-25th centile) and head circumference 53.5 cm (50-75th centile)). Craniofacial dysmorphism included low set ears with rather large ear lobes, mild bitemporal narrowing, horizontal eyebrows, upslanting palpebral fissures, midfacial hypoplasia, bulbous nose, prominent columella, short philtrum, highly arched palate, hypotonic large mouth with protruding large tongue, thick hair and short neck. Further minor anomalies were mild camptodactyly, tapered fingers, sandal gaps and a lumbar hyperlordosis. At that time she spoke simple 2–3 word sentences with a blurred pronunciation. She had deficits in fine motor skills but had been able to bike since the age of ~11 years old. She was reported to have diminished pain sensitivity and a low frustration tolerance with aggressive outbursts. She attended a school for children with special needs 3 days a week where she was successfully integrated. Since the age of 12 years she received surgical and conservative orthodontic therapy. Puberty development was normal with menarche at 13 years. Vision and hearing were reported to be normal.

At last investigation at the age of 14 years and 3 month she presented with inappropriate laughter, stereotypic hand movements, skin picking, truncal obesity, kyphoscoliosis and cold extremities. She still showed the open mouth appearance and protruding tongue. Due to her facial appearance Kleefstra syndrome or a chromosomal imbalance was considered. While chromosomal microarray analysis (CMA) showed normal results, trio whole exome sequencing (WES) revealed a pathogenic truncating *de novo* mutation c.2504delC (p.(Pro835Leufs*46)) in exon 14 of *MED13L* (NM_015335.4), as well as a *de novo* heterozygous variant of uncertain significance c.244A>C (p.(Ile82Leu)) in exon 1 of *POMT2* (NM_013382.5) with mainly benign predictions. Mutations in *POMT2* are known to cause autosomal recessive forms of muscular dystrophy-dystroglycanopathies (MIM #613150, #613156 and #613158), but a second rare, likely pathogenic variant in *POMT2* could not be detected in this patient. In addition, there was no sign of relevant muscular phenotype in the patient which may indicate no influence of the *POMT2* variant on the phenotype of our patient.

3.2. Patient 2

Patient 2 (Fig. 1I–L), a 6.5-year-old boy, is the first child of healthy non-consanguineous parents, aged 32 (mother) and 33 (father) at the time of conception. His younger sister is healthy. He was born at term after a pregnancy complicated by maternal herpes zoster and preeclampsia. Despite some meconium inhalation, apgar scores have been reported to be good. Birth weight and length were 4.1 kg (75th centile), 57.8 cm (>95th centile) respectively. Head circumference was reported to be below average. After birth, he was reported to have a murmur but cardiac evaluation showed no congenital heart defect.

Since the beginning, he had problems with breast feeding and had ankyloglossia. At age 6 months, he was noted to be hypotonic with delayed milestones. He started commando crawling at age 1 year and walked independently at age 2 years. He had a brain MRI at the age of 4.5 years showing mild dilatation of the lateral ventricles and a segmental thinning of the posterior part of the body of the corpus callosum. At the age of 6.5 years, he had a head circumference of 51 cm (25th centile) and his facial anomalies included squared, low set ears with rather narrow ear lobes, mild ptosis, flat malar region, mild broadening of the nose, and retrognathia (Fig. 1I–J). He attended a preschool for children with

Table 1
Summary of the reported patients with chromosomal aberrations or gene variants of *MED13L*.

Reference Patient's Age and Gender	Neurological Features	Brain MRI Findings	Craniofacial Dysmorphic Features	Cardiac Manifestations	Other Features	Aberration/ Mutation	Prediction	Frequency in Control Databases	Remarks
(Muncke et al., 2003) 7 years, female	ID, nearly absent speech, mild motor delay, ataxia	no structural abnormalities, advanced myelinization	postnatal microcephaly, facial features: NR	dTGA, pVSD open foramen ovale, mild CoA	NR	t (12; 17) (q24.1; q21) *de novo* between exon 1 & 2	likely truncating	–	This study introduced 5 new exons to the previously nominated *KIAA1025*, designating the novel *MED13L* gene which they called *PROSIT240*. They also provided the first link of the gene to ID and congenital heart defects.
(Muncke et al., 2003) NR, NR	NR	NR	NR	dTGA	NR	c.752A>G p.(Glu251Gly) *maternally inherited* exon 6	*SIFT:* damaging *PolyPhen-2:* possibly damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	
(Muncke et al., 2003) NR, NR	NR	NR	NR	dTGA	NR	c.5615G>A p.(Arg1872His) *inheritance: NR* exon 25	*SIFT:* tolerated *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: A = 0.02% ESP6500_AA: A = NR ESP6500_EA: A = 0.01% ExAC: NR	
(Muncke et al., 2003) NR, NR	NR	NR	NR	dTGA	NR	c.6068A>G p.(Asp2023Gly) *inheritance: NR* exon 28	*SIFT:* tolerated *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	
(Najmabadi et al., 2011) (2 siblings) NR, NR	mild ID	NR	NR (non-syndromic)	NR	NR	c.4247G>A p.(Arg1416His) *homozygous* exon 19	*SIFT:* damaging *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study targeted deep sequencing was performed in 136 consanguineous families with undiagnosed ID.
(Iossifov et al., 2012) NR, male	autism spectrum	NR	NR	NR	NR	c.5364+1dupG *inheritance: NR* intron 23-24	*MaxEntScan:* 9.7 > 8.1 *GeneSplicer:* 5.7 > 3.4 *HSF:* 94.9 > 85.8	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study WES was performed for *de novo* mutations in 343 families with sporadic autism spectrum.
(Asadollahi et al., 2013) Patient 1 4 years, female	moderate ID, severe expressive speech delay, hypotonia, gross and fine motor coordination problems, reported to have good sense of humor	normal MRI	broad forehead, slightly asymmetric face, large, low set ears, bitemporal narrowing, upslanting palpebral fissures, long eyelashes, flat nasal root, bulbous nose, deep philtrum, micrognathia, hypotonic open mouth, macroglossia	supracardial TAPVC, pulmonary atresia, VSD, multifocal pulmonary perfusion	anteriorly positioned anus	17 kb deletion *de novo* exon 2	likely truncating	DGV: absent	This study for the first time delineated the *MED13L* haploinsufficiency syndrome and suggested it as a neurocristopathy to be considered in the differential diagnosis of DiGeorge/ Velo-cardio-facial/ 22q11.2 deletion syndrome.
(Asadollahi et al., 2013) Patient 2 ~3 years, female	severe DD, absent speech, hypotonia	NR	broad forehead, large, low set ears, bitemporal narrowing, upslanting palpebral fissures, flat nasal root, bulbous nose, deep and short philtrum, micrognathia, hypotonic open mouth	TOF	bowed legs, overlapping of the fifth toe over the fourth toe	115 kb deletion *de novo* exons 3-4	likely truncating	DGV: absent	

(*continued on next page*)

Table 1 (*continued*)

Reference Patient's Age and Gender	Neurological Features	Brain MRI Findings	Craniofacial Dysmorphic Features	Cardiac Manifestations	Other Features	Aberration/ Mutation	Prediction	Frequency in Control Databases	Remarks
(Asadollahi et al., 2013) Patient 3 6.5 years, female	learning difficulties, neonatal muscular hypotonia, unsteady gait for a long time	NR	broad nasal bridge	pVSD	mild pectus excavatum	1 Mb triplication *de novo* including the entire *MED13L* and *MAP1LC3B2* genes	likely overexpression	DGV: absent	
(van Haelst et al., 2015) Patient 1 3.5 years, female	global DD, transient hypertonia of all extremities at the age of 14 months	normal MRI	broad forehead, slightly asymmetric face, upslanting palpebral fissures, bulbous nose, hypotonic open mouth, macroglossia	excluded	bilateral accessory nipples, clubfoot, abnormal palmar creases with an extra phalangeal crease of the index fingers	c.480-1G>T *de novo* intron 4-5	RNA study showed deletion of 15 amino acids (160–174) in the conserved N-terminal domain	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	This study reported further patients supporting the *MED13L* haploinsufficiency syndrome.
(van Haelst et al., 2015) Patient 2 4.5 years, male	global DD, no behavioral problems	NR	small eyelids, mild retrognathia, hypotonic open mouth	small PFO	neonatal feeding problems, eczema and gastroesophageal reflux	41 kb deletion *de novo* exons 6–20	in-frame but likely resulting in loss of protein function	DGV: absent	
(Gilissen et al., 2014) NR, NR	moderate ID, epilepsy	NR	small dysplastic low-set ears, bulbous nasal tip, large mouth	NR	single transverse palmar crease of the right hand	c.2579A>G p.(Asp860Gly) *de novo* exon 15	*SIFT:* tolerated *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study whole genome sequencing was performed in 50 families with sporadic undiagnosed severe ID.
(Redin et al., 2014) NR, male	moderate ID, hypotonia	NR	open mouth appearance	excluded	NR	c.6118_6125del p.(Gly2040Asnfs*32) *de novo* exon 28	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study targeted high-throughput sequencing of 217 genes in 106 undiagnosed ID patients was performed.
(Utami et al., 2014) 14 years, female	moderate ID, absent speech, absence seizures	ventricular enlargement in correlation with global atrophy	Pierre–Robin sequence at birth, flat occiput, hypertelorism, broad nasal bridge, bulbous nose, flat philtrum	excluded	strabismus, hirsutism, scoliosis during puberty, metatarsus adductus of the thumb, bilateral equinovarus foot deformity	t (12; 19) (q24; q12) *de novo* intron 4	likely truncating	–	This study showed defective migration of cranial neural crest cells after knockdown of *MED13L* orthologue in zebrafish.
(Hamdan et al., 2014) 5 years, female	moderate global ID, no seizure, no autistic features, no behavioural problems	increased CSF spaces in brain CT	NR	excluded	overweight, strabismus	c.1708_1709delCT p.(Ser570Phefs*27) *de novo* exon 10	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study WES was performed for *de novo* mutations in 41 families with sporadic moderate to severe ID.
(Iglesias et al., 2014) 17 years, NR	DD	NR	NR	NR	NR	c.2239-10_2270del142insATTA p.? *de novo* intron 11 and exon12	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study WES was used for routine clinical practice in 115 patients mainly with birth defects and DD.

(Cafiero et al., 2015) Patient 1 8 years, female	moderate DD, severe speech impairment, hypotonia, ataxic gait, friendly behavior, no seizure	no abnormalities	brachycephaly, high forehead, horizontal eyebrows, long eyelashes, depressed nasal bridge, mid-face hypoplasia, thin upper vermilion border, prognathism	excluded	cleft palate, clubfoot	c.3765delC p.(Cys1256Valfs*2) *de novo* exon 17	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	This study suggested to consider the *MED13L* haploinsufficiency syndrome in the differential diagnosis of the 1p36 microdeletion syndrome.
(Cafiero et al., 2015) Patient 2 3 years, female	moderate global DD, one episode of febrile seizures	NR	mild brachycephaly, high forehead, bitemporal narrowing, horizontal eyebrows, upslanting palpebral fissures, synophrys, epicanthus, depressed nasal bridge, bulbous nasal tip, mid-face hypoplasia, deep philtrum, cupid-bow upper lip, prognathism and anteverted ears with thick helix	PFO	esotropia	c.607dupT p.(Ser203Phefs*32) *de novo* exon 5	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	
(Cafiero et al., 2015) Patient 3, 12 years, female	moderate global DD, walking with flexed knees and difficulties with tandem gait and hopping, choreiform movements of upper and lower extremities with a milkmaid's grip, sociable without behavioural difficulties, seizures	T2-hyperintense foci in periventricular and subcortical white matter, stable underlying low white matter volume	macrocephaly, prominent and square forehead with frontal bossing and a high anterior hairline, left ptosis, epicanthic folds, upslanting palpebral fissures, depressed nasal bridge, bulbous nasal tip, prognathism, a right ear pit, protuberant lower jaw with a relatively large tongue	excluded	central obesity, tapered fingers, long toes with lateral deviation of the second toes, cubitus valgus and lumbar lordosis	c.4420A4T p.(Lys1474*) *de novo* exon 20	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	
(Adegbola et al., 2015) Patient 1 11 years, female	mild to moderate ID, severe language and motor delay, muscular hypotonia, poor coordination without ataxia, normal non-autistic behavior	NR	brachycephaly, frontal bossing, low hair line, triangular face, low set ears, bitemporal narrowing, upslanted palpebral fissures, hypertelorism, ptosis, flat nasal bridge, bulbous nose, macrostomia, widely spaced teeth, prognathism, short neck	excluded	myopia, high arched palate, bilateral cubitus valgus, adduction of feet, cryptorchidism	180 kb duplication *de novo* exons 2-4	likely truncating	DGV: absent	This study reported a larger series of patients highlighting the reduced penetrance of congenital cardiac defects in *MED13L* haploinsufficiency syndrome.
(Adegbola et al., 2015) Patient 2 3 years, male	moderate ID, severe language and motor delay, muscular hypotonia, facial hypotonia with drooling, hyperreflexia without spasticity or pyramidal signs, ataxia, autistic behaviors	myelination delay	broad forehead, low set, posteriorly rotated ears with an uplift of the ear lobule, mild bitemporal narrowing, epicanthal folds, flat and broad nasal bridge, rounded nasal tip, broad columella, marked philtrum and full lips	excluded	fifth finger clinodactyly, unilateral cryptorchidism	125 kb deletion *de novo* exons 3-4	likely truncating	DGV: absent	
(Adegbola et al., 2015) Patient 3 4 years, female	moderate ID, severe speech delay, motor delay, no autistic behavior	a short and thick corpus callosum, a cyst from cavum vergae and an arachnoid cyst	plagiocephaly, brachycephaly, frontal bossing, frontal hair upsweep, large anterior fontanel, preauricular tags, facial asymmetry, upslanting palpebral fissures, hypertelorism, macrostomia, short neck	excluded	severe hyperopia, astigmatism, congenital torticollis	64 kb duplication *de novo* exons 5-28	likely truncating	DGV: absent	
(Adegbola et al., 2015) Patient 4 15 years, male	moderate ID, severe speech delay, muscular hypotonia, an uncoordinated gait, agitation, restlessness, overfriendliness and hyperactivity, one time neonatal seizure	normal MRI	frontal bossing, frontal hair upsweep, thick eyebrows with medial flare, low set ears, upslanting palpebral fissures, wide and depressed nasal bridge, broad nasal tip, bulbous macrostomia with thick lip vermilion, wide and often open mouth with downturned corners	excluded	congenital pneumonia, arthrogryposis of the hands, ulnar deviated club hands, camptodactyly of the toes, cutaneous syndactyly of toes 2–3	296 kb duplication *de novo* exons 2-26	likely truncating	DGV: absent	

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Table 1 (*continued*)

Reference Patient's Age and Gender	Neurological Features	Brain MRI Findings	Craniofacial Dysmorphic Features	Cardiac Manifestations	Other Features	Aberration/ Mutation	Prediction	Frequency in Control Databases	Remarks
					and decreased palmar creases				
(Adegbola et al., 2015) Patient 5 3 years, female	mild to moderate ID, global DD, muscular hypotonia, aggressive behavior	periventricular small round signal alterations (myelination defect)	broad forehead, slight uplift of the ear lobules, slight bitemporal narrowing, epicanthal folds, broad nasal bridge, rounded nasal tip, macrostomia, marked philtrum, full lips	excluded	hypermetropia, strabismus, bilateral clinodactyly of the fifth rays of hands	276 kb deletion *de novo* exons 2-22	likely truncating	DGV: absent	
(Adegbola et al., 2015) Patient 6 6 years, female	mild to moderate ID, speech delay, autistic behavior, multifocal epileptiform discharges	normal MRI	hypertelorism, flat midface	PFO	bilateral high-tone hearing loss, simian crease, short thumbs, umbilical hernia	c.5949_5950delGA p.(Gln1984Alafs*31) *de novo* exon 27	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	
(Adegbola et al., 2015) Patient 7 8 years, male	learning disability but no ID, global DD	normal MRI	triangular face, low set ears with irregular antihelices, short philtrum, prominent columella, and widely spaced teeth	PFO	unilateral conductive hearing loss, pectus excavatum	3 Mb duplication *Maternally inherited* including the entire *MED13L* gene as well as 11 other genes (cosegregating with facial anomalies)	likely overexpression	DGV: absent	
(Adegbola et al., 2015) Patient 8 4 years, female	moderate ID, speech delay, motor delay	normal MRI	brachycephaly, frontal bossing, round face, low set and posteriorly rotated ears, bitemporal narrowing, upslanted palpebral fissures, deeply set eyes, horizontal and laterally extended eyebrows, depressed nasal bridge, bulbous nose, open mouth with downturned corners	VSD	inverted and hypoplastic nipple, anteriorly placed anus	1.9 Mb deletion *de novo* including the entire *MED13L* gene as well as seven other genes	likely truncating	DGV: absent	
(Codina-Sola et al., 2015) Patient 1 NR, NR	severe ID, no functional language, hypotonia, autism, sleep disturbance, no seizure	NR	not specified but reported to be present and similar to patients 1 and 2 of Asadollahi et al., 2013	NR	umbilical hernia	c.1708_1709delAG p.(Ser570Phefs*27) *de novo* exon 10	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	This patient harbors the same mutation reported by Hamdan et al., (2014). In this study integrated WES and transcriptome analysis was performed in males with autism spectrum.
(Codina-Sola et al., 2015) Patient 2 NR, NR	moderate ID, no functional language, autism, no seizure	NR	no dysmorphic features	NR	NR	c.A5371T p.(Ser1791Cys) *paternally inherited* exon 24	*SIFT:* damaging *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: 0.002% for C but NR for T	Pathogenicity of this mutation was reported to be unclear and the patient had also a stop mutation in *MSLN*.
(Caro-Llopis et al., 2016) Patient 2 8 years, male	global DD, hypotonia, poor coordination, autism spectrum, autoaggression, no seizure	prominence of subarachnoid space, ventriculo-megaly and mega cisterna magna.	low set ears, hypertelorism, downslanting palpebral fissures, bilateral epicanthus, left eye ptosis, depressed nasal bridge, tented upper lip, frequent drooling	PDA	strabismus, unilateral hearing loss, atopic dermatitis	c.5695G>A p.(Gly1899Arg) *de novo* exon 25	*SIFT:* damaging *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study trio targeted NGS was performed in 3 unrelated patients, which led the identification of mutations in *MED12* (their patient 1) and *MED13L* (their patients 2 and 3). The same cases are presented in the study of Martínez et al., (2017) evaluating the molecular aetiology in 92 patients with syndromic ID by targeted NGS.
(Caro-Llopis et al., 2016) Patient 3 24 years, male	mild ID, global DD, hypotonia, poor coordination	NR	frontal bossing, low set hair, synophrys, low set ears, downslanting palpebral fissures, epicanthus, depressed nasal bridge, bulbous nose, narrow palate, wide gingival fold, abnormal implantation of teeth, retrognathia	excluded	strabismus, hypertrichosis, kyphosis, pes cavus deformity, joint hyperlaxity, unilateral renal agenesis	c.2524C>T p.(Arg842*) *de novo* exon 14	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	

(Wang et al., 2016) NR, female	DD, hypotonia, autism spectrum, sleep problems, no seizure	NR	mandibular protrusion	NR	hyperopia	c.2395_2396delCA p.Gln799Glyfs*10 *de novo* exon 13	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	In this study, single-molecular inversion probes and targeted sequencing of selected autism risk genes was performed in 1543 Chinese autism probands.
(Yamamoto et al., 2017) Patient 1 2 years, female	severe DD, no speech hypotonia, motor delay	lesions of differential intensity in the periventricular area of the occipital white matter with T1 low and T2 high intensity	frontal bossing, low set ears, horizontal eyebrows, upslanting palpebral fissures, flat nasal bridge, midface hypoplasia, bulbous nose, pointed chin	excluded	high-arched palate	c.257delT p.(Phe86Serfs*9) *de novo* exon 2	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	Patients 2 and 3 in this case report are siblings with a recurrent intragenic deletion due to maternal mosaicism.
(Yamamoto et al., 2017) Patient 2 5 years, female	mild DD, hypotonia, motor delay and incoordination	no abnormalities	craniosynostosis, microcephaly, round face, horizontal eyebrows, upslanting palpebral fissures, depressed nasal bridge	excluded	growth deficiency	deletion *maternally inherited (<1% mosaicism in the mother)* exons 3-14	likely truncating	DGV: absent	
(Yamamoto et al., 2017) Patient 3 (sister of patient 2) 17 months, female	moderate DD, hypotonia, motor delay and incoordination	no abnormalities	round face, low set ears, downslanting palpebral fissures, flat nasal bridge, midface hypoplasia, short philtrum	excluded	high-arched palate	deletion *maternally inherited (<1% mosaicism in the mother)* exons 3-14	likely truncating	DGV: absent	
This study; Patient 1 14 years, female	moderate ID, severe speech delay, motor delay, hypotonia, deficits in fine motor skills, absence seizures with eyelid myoclonia treated with Orfiril, aggressive outbursts, inappropriate laughter and stereotypic hand movements at the age of ~14 years	not available	low set ears, mild bitemporal narrowing, upslanting palpebral fissures, horizontal eyebrows, midface hypoplasia, bulbous nose, prominent columella, highly arched palate, hypotonic mouth with protruding tongue, retrognathia, short neck	excluded	neonatal gastroesophageal reflux disease, club feet and pes adductus, mild camptodactyly, tapered fingers, sandal gap, lumbar hyperlordosis, kyphoscoliosis, truncal obesity	c.2504delC p.(Pro835Leufs*46) *de novo* exon 14	likely truncating	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	This case provides a follow-up into early adulthood of a patient with *MED13L* haploinsufficiency syndrome.
This study; Patient 2 6.5 years, male	global DD, absent speech, infantile muscular hypotonia, some clumsiness, sleep problems, poor attention span, epilepsy	mild dilation of the lateral ventricles and a segmental thinning of the posterior part of the body of the corpus callosum	squared, low set ears with rather narrow ear lobes, mild ptosis, flat malar region, mild broadening of the nose, and retrognathia	excluded	some hyperlaxity of the joints and skin of extrimities	c.2579A>G p.(Asp860Gly) *de novo* exon 15	*SIFT:* tolerated *PolyPhen-2:* probably damaging *Mutation Taster:* disease causing	1000 Genomes: NR ESP6500_AA: NR ESP6500_EA: NR ExAC: NR	This patient harbors the same mutation reported by Gilissen et al., (2014).

CoA: coarctation of the aorta; CSF: cerebrospinal fluid; DD: developmental delay; DGV: Database of Genomic Variants; dTGA: dextro-looped transposition of the great arteries; ESP6500: National Heart, Lung, and Blood Institute [NHLBI] GO Exome Sequencing Project 6500, AA: African-American, EA: European-American; ExAC: Exome Aggregation Consortium; pVSD: perimembranous ventricular septal defect; ID: intellectual disability; NGS: next generation sequencing; NR: not reported; PDA: patent ductus arteriosus; PFO: patent foramen ovale; TAPVC: total anomalous pulmonary venous connection; TOF: tetralogy of Fallot; WES: whole exome sequencing.

Table 2
Frequency of major clinical features in described patients (26 cases including this study) with likely truncating/LOF aberrations of *MED13L*.

Clinical Feature	Number of Patients	Percentage
ID or DD	26/26	100%
Severe speech delay	11/22	50%
Autistic features	5/25	20%
Hypotonia	15/25	60%
Coordination problems	9/24	38%
Seizures or abnormal EEG	4/25	16%
Aggressive behavior	2/22	9%
Abnormal MRI	6/16	38%
Strabismus	3/24	13%
Facial dysmorphism	21/21	100%
broad/prominent forehead	16/21	76%
low set ears	11/21	52%
bitemporal narrowing	9/18	50%
horizontal eyebrows	6/21	29%
upslanting palpebral fissures	13/21	62%
depressed/flat nasal bridge	18/21	86%
bulbous nose	15/21	71%
abnormal chin (micro-/pro-/retro-gnathia)	12/22	55%
macroglossia	6/21	29%
Complex congenital heart defects	3/23	13%
Persistent foramen ovale/ventricular septal defect	4/23	17%
Abnormal growth parameters	10/20	50%
microcephaly	3/20	15%
macrocephaly	1/20	5%
low birth weight	3/20	15%
postnatal underweight	3/20	15%
postnatal overweight	1/20	5%

The above features are according to the description of the patients in the literature, if a feature has not been documented, it is neither counted to be present nor absent. DD: developmental delay; ID: intellectual disability.

disabilities and received speech therapy at home once a week but had no speech except using sounds and two-syllable gesturing to communicate. He could follow simple commands and tell two body parts (ears, nose) on himself and others. He had poor attention span overall but could spend a lot of time on his iPad and could spell on the iPad, type letters, read whole words, point to written numbers and read simple books but could not draw at all. He knew his name and his parents as opposed to strangers. He gave much affection to his family, played appropriately with toys but enjoyed computer most of all. He was almost completely toilet trained. His hearing and vision were considered to be normal and detailed eye examination had shown no retinal abnormality. He had some sleep problems which improved with small dose of melatonin and sometimes Benadryl. He had no muscle weakness, could run, and walk up and down stairs quite well, but was still clumsy. His extremities showed some hyperlaxity of the joints and skin. He had no known cardiac, pulmonary, renal, gastrointestinal or skeletal abnormalities. Shortly after, he developed intractable epilepsy and despite triple medications still has multiple seizures every day. While urinary organic acid, plasma amino acids and CMA were normal, trio WES analysis revealed a likely pathogenic *de novo* missense mutation c.2579A>G (p.(Asp860Gly)) in exon 15 of *MED13L* (NM_015335.4). This mutation was predicted to be deleterious by the majority of prediction tools. Mutation modelling as described in the methods predicted Asp860 to be located in an α-helical sequence stretch spanning residues Val858-Met864 and replacement of Asp860 by a flexible glycine decreases the helix stability thereby affecting the secondary structure of MED13L. In addition, Asp860 is in close proximity to the experimentally confirmed phosphorylation site Thr867. The Asp860Gly exchange is located within the recognition site for various kinases and is predicted to affect the specificity of Thr867 phosphorylation.

4. Methods

Genetic studies were performed on DNA extracted from peripheral blood. CMA in patient 1 was performed using Affymetrix Cytoscan HD array as described previously (Asadollahi et al., 2014). CMA in patient 2 was commissioned to an external service (Quest Diagnostics, TX) using Postnatal, ClariSure® Oligo-SNP Test (2.67 million probes, resolution 1.15 kb). WES in patient 1 and her parents was performed using the Agilent SureSelect XT Clinical Research Exome Kit (V5) on an Illumina HiSeq 2500 System (Illumina, San Diego, CA) with 125 bp paired end reads. About 98% of the targeted bases were assessed by $\geq$ 20 sequence reads. The WES data were analyzed using the NextGENe Software (SoftGenetics, State College, PA) for non-silent exonic and splice site *de novo* variants. Candidate nucleotide variants from WES were also confirmed by Sanger sequencing after PCR amplification from patient's DNA using an ABI3730 capillary sequencer (Applied Biosystems, Foster City, CA). The *POMT2* gene was also screened for exonic CNVs using the copy number variation detection tool of SeqNext (JSI Medical Systems, Kippenheim, Germany). WES in patients 2 and his parents were commissioned to an external service (GeneDx Laboratory, Gaithersburg, MD) using the Agilent Sure Select XT2 kit for targeting on a HiSeq 2000 System (Illumina Inc.) with 100 bp paired end reads. The two *MED13L* variants have been submitted to ClinVar (http://www.ncbi.nlm.nih.gov/clinvar) with accession numbers of SCV000579469 and SCV000579470, respectively. Secondary structure predictions were performed using the consensus secondary structure prediction provided by the NPS@ server (Combet et al., 2000). Experimentally verified phosphorylation sites were obtained from PhosphositePlus (Hornbeck et al., 2012). Candidate kinases and phosphorylation propensities were predicted using the GPS 3.0 prediction tool (Xue et al., 2005).

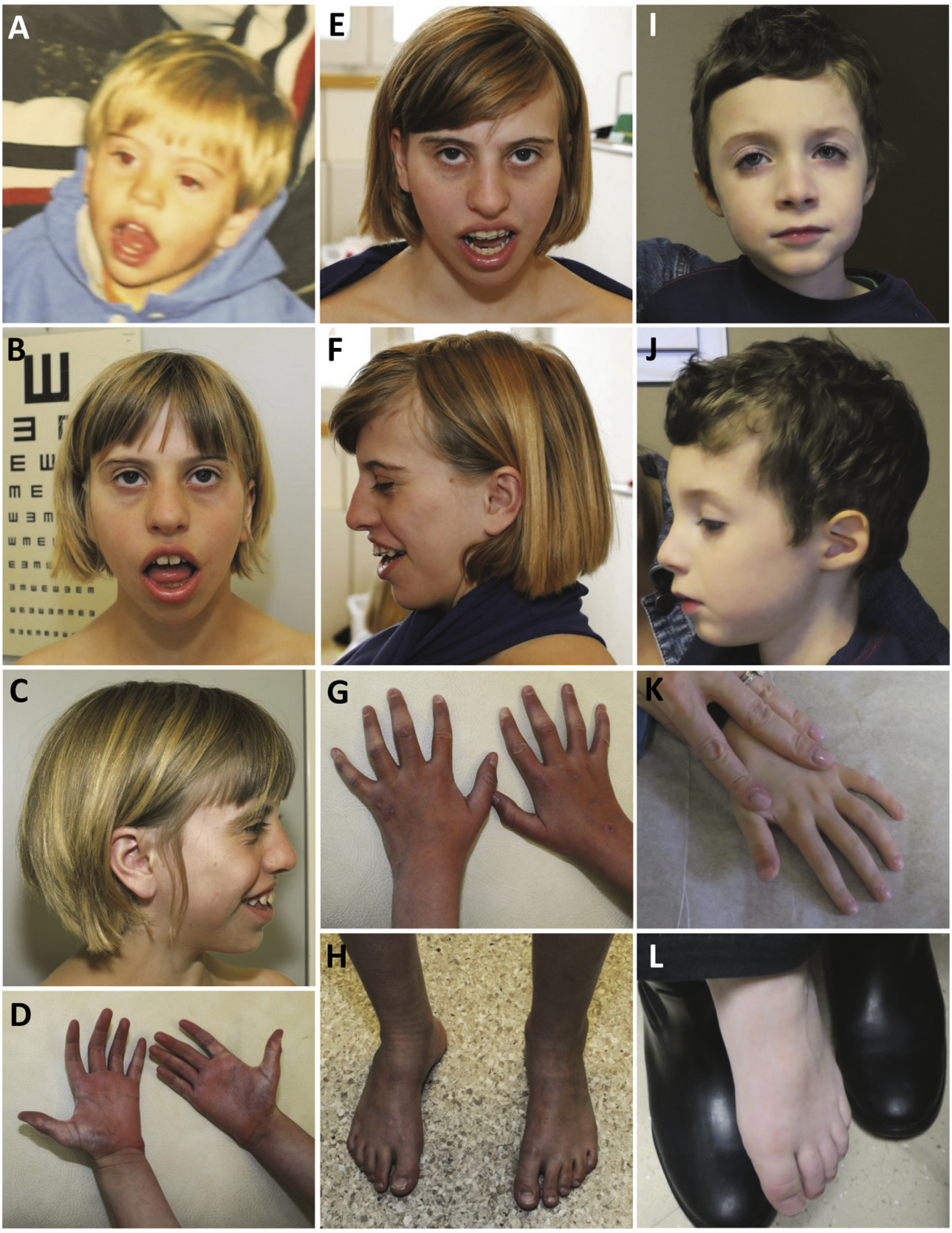

Fig. 1. Phenotypes of our new patients with *de novo* mutations in *MED13L*. A-H Patient 1: Facial gestalt in early childhood (A), facial appearance, hands and feet at the age of 11 years and 7 months (B-C, D, G-H), and facial gestalt at the age of 14 years and 3 months (E, F). I-L Patient 2: Facial gestalt, hand and foot at the age of 6.5 years.

5. Phenotypic spectrum in *MED13L* defects

A decade after the initial report of a *de novo MED13L*-disrupting translocation in a girl with ID and dTGA (Muncke et al., 2003), availability of genome-wide testing brought *MED13L* into the attention of medical geneticists. In 2013, we described two patients with *de novo* out-of-frame deletions within *MED13L* presenting with ID, speech delay, muscular hypotonia and complex congenital heart defects as well as similar facial features of broad forehead, bitemporal narrowing, low set ears, upslanting palpebral fissures, flat nasal root, bulbous nose, and hypotonic open mouth delineating a recognizable *MED13L* haploinsufficiency syndrome (Asadollahi et al., 2013). This finding was then further confirmed following the report of two phenotypically similar patients by van Haelst et al. (2015), harbouring *de novo* likely LOF variants of *MED13L* (Table 1) and three further patients with disrupting translocation (Utami et al., 2014), or truncating mutations (Hamdan et al., 2014; Redin et al., 2014) (Table 1) with comparable neurodevelopmental and facial features. To date, 26 patients with likely truncating/LOF *de novo* aberrations of *MED13L* have been reported, all showing ID/developmental delay (DD) and a spectrum of facial anomalies (Tables 1 and 2). In about half or more of the patients, severe speech delay and hypotonia, as well as the following facial anomalies were reported: broad/prominent forehead, low set ears, bitemporal narrowing, upslanting palpebral fissures, depressed/flat nasal bridge, bulbous nose, and abnormal chin (Table 2). Abnormal MRI findings of myelination defects and abnormal corpus callosum, ataxia and coordination problems, autistic features and seizures/abnormal EEG, congenital heart defects, as well as horizontal eyebrows and macroglossia are also common signs present in about 20–50% of the patients (Table 2). Less common traits include strabismus, aggressive behaviours, cleft palate, truncal obesity, umbilical hernia and a range of skeletal features such as club feet. Half of the cases with available information have shown an abnormal growth parameter such as micro- or macrocephaly, or under- or overweight (Table 2).

The initially described complex congenital heart phenotype has been so far observed in three patients (Asadollahi et al., 2013; Muncke et al., 2003) and therefore as also concluded by Adegbola et al. (2015), should be considered among variable features with incomplete penetrance and without obvious genotype-phenotype correlation. The latter is substantiated by the fact that of the two patients with similar deletion of exons 3–4, one had a normal heart (Adegbola et al., 2015) while the other had a complex heart disease (Asadollahi et al., 2013). Of note, Muncke et al. also reported three candidate missense mutations found in patients with dTGA (Muncke et al., 2003), a finding which has not been replicated so far. A screening of reported mutations including one of the *MED13L* variants from Muncke et al. (2003) (c.752A>G, p.(Glu251Gly); maternally inherited) in 102 Chinese patients with dTGA (Lei et al., 2014) did not identify this variant in an additional case. A genome-wide association study identified significant association of a variant (rs11067763) near *MED13L* with blood pressure in a Chinese population (Lu et al., 2015) with undetermined clinical significance.

The growing number of described patients along with the results of the Deciphering Developmental Disorders Study (DDD-Study, 2015) highlighting *MED13L* as one of the most common eight disease causing genes each accounting for 0.5–1% of >1000 children with undiagnosed developmental disorders, indicate the importance of *MED13L* haploinsufficiency as a frequent cause of syndromic ID. According to the clinical reports, *MED13L* haploinsufficiency has also sparked resemblance to more common neurodevelopmental disorders such as 22q11.2 deletion syndrome (Asadollahi et al., 2013), mosaic trisomy 21, Kleefstra syndrome (patient 1 of this study) and 1p36 deletion syndrome (Cafiero et al., 2015), as well as MED12-related Opitz-Kaveggia syndrome (Adegbola et al., 2015; Caro-Llopis et al., 2016).

Notably, two patients have been reported with gains of the whole gene, one with a *de novo* triplication of *MED13L* and the adjacent *MAP1LC3B2* (Asadollahi et al., 2013), and the other with a maternally inherited duplication of *MED13L* and 11 neighbouring genes (Adegbola et al., 2015), both presenting with some learning difficulties but no ID. This observation highlights the fact that in the *MED13L* haploinsufficiency syndrome like in some other haploinsufficiency syndromes, copy number gain of the gene results in a milder neurodevelopmental phenotype.

In contrast to the likely LOF mutations (Fig. 2), interpretation of *MED13L* missense variants is still challenging. The two so far reported *de novo* missense mutations including the p.(Gly1899Arg) in a patient of Caro-Llopis et al. (2016), as well as the p.(Asp860Gly) mutation reported in a patient of Gilissen et al. (2014) and in our

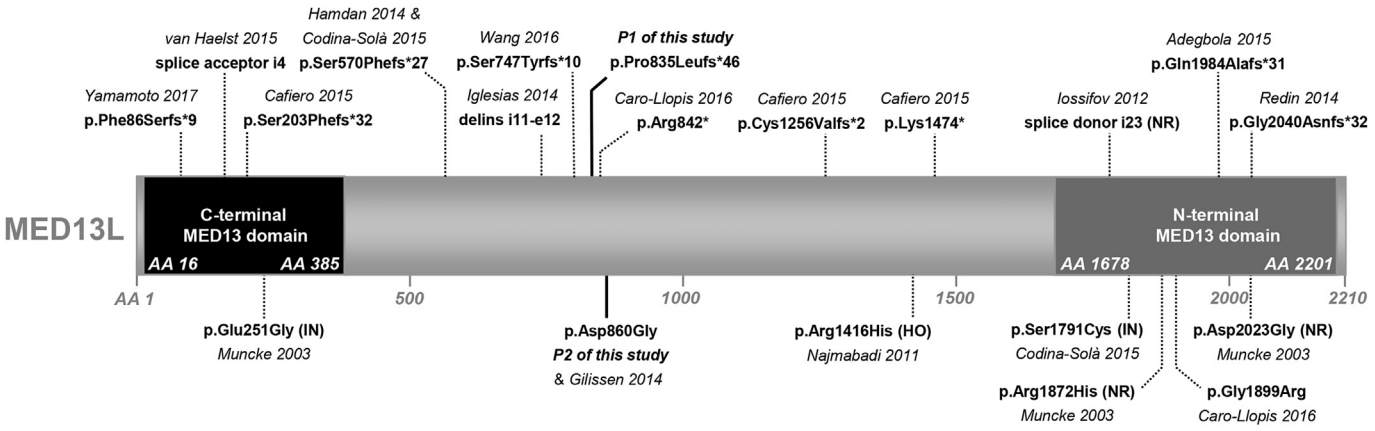

Fig. 2. Schematic representation of MED13L uncharacterized structure with conserved C- and N-terminal domains (according to NCBI's conserved domain database (NP_056150.1) (Marchler-Bauer et al., 2015)). The position of mutations identified in our patients and those reported in the literature are depicted: truncating and splice site mutations are plotted above the protein scheme, and missense variants are shown below. The majority of the mutations occurred *de novo* and heterozygous, elsewise additional information are given in parentheses (HO: homozygous, IN: inherited, NR: inheritance not reported, i: intron, e: exon).

unrelated patient 2 are likely disease-causing (Fig. 2, Table 1). The recurrent p.(Asp860Gly) mutation locates outside the N- and C-terminal domains and is predicted by our mutation modelling to decrease the helix stability thereby affecting the secondary structure of MED13L, while the p.Gly1899 affects the N-terminal domain. Like the patients with LOF mutations, these three patients also demonstrate phenotypic variability despite having ID and some of the facial characteristics. Notably, the two patients with p.(Asp860Gly) mutation developed epilepsy. The other reported missense mutations including the three heterozygous missense mutations (one maternally inherited and two with unknown inheritance) in three dTGA patients (Muncke et al., 2003), the homozygous missense mutation in two siblings of a consanguineous family with non-syndromic ID (Najmabadi et al., 2011) and the heterozygous missense mutation (paternally inherited) in a patient with non-syndromic ID (Codina-Sola et al., 2015) (Table 1) may only be considered as variants of uncertain significance with current state of knowledge.

6. Biological roles of MED13L

MED13L, a protein with uncharacterized structure (Fig. 2), is a subunit of the Mediator complex which links DNA-binding transcription factors and RNA polymerase II for gene transcription (Sato et al., 2004). Mediator is an evolutionarily conserved multiprotein complex which plays diverse and dynamic roles at multiple stages of transcription (Yin and Wang, 2014). This complex in Mammals contains >30 subunits (Table 3) arranged in four structurally distinct modules of head, middle and tail, representing the main complex core, and a kinase module which interacts variably with the core (Casamassimi and Napoli, 2007; Conaway and Conaway, 2013). The kinase module which serves in both transcriptional repression and activation roles (Carrera et al., 2008; Elmlund et al., 2006; Samuelsen et al., 2003; Schiano et al., 2014) contains MED12/12L, MED13/13L, cyclin-dependent kinase 8/19 (CDK8/19) and Cyclin C. It has been shown that the kinase module links physically to the core via MED13/MED13L (Davis et al., 2013; Knuesel et al., 2009; Taatjes, 2010) and dissociates after SCF-Fbw7 dependent ubiquitylation and degradation of MED13/MED13L (Davis et al., 2013). Therefore, haploinsufficiency of *MED13L* may in fact affect the link between the kinase module and the core disturbing the transcriptional regulations.

Accumulating evidence suggest specialized function for the individual Mediator components through binding to specific transcription factors (Kim et al., 2004; Poss et al., 2013; Uwamahoro et al., 2012) or through complex-independent roles as assumed for MED12 as a regulator of TGFβ signaling (Huang et al., 2012; Poss et al., 2013). Accordingly, knockout and mutant mice of various individual subunits, display different phenotypes as well as mortality at different developmental stages (Yin and Wang, 2014). These data in addition to the distinct phenotypes of patients with defects of different mediator subunits (Table 3) suggest their cell-, pathway-and time-specific function especially during the development of the nervous system. Therefore, characterizing possible target genes for MED13L is crucial for understanding the underlying pathomechanisms.

MED13L is expressed in multiple human tissues (Muncke et al., 2003; Utami et al., 2014), which is consistent with its role in the association of core Mediator with alternative kinase modules together with MED13 (Davis et al., 2013; Knuesel et al., 2009; Taatjes, 2010) but has been shown to have relatively higher expression in the fetal and adult brain especially in cerebellum, heart and skeletal muscle (Muncke et al., 2003; Utami et al., 2014).

Using a genome-wide short hairpin RNA screen for the identification of novel cofactors required for retinoblastoma tumor suppressor (Rb)/E2F-mediated inhibition of cell proliferation, Angus et al (Angus and Nevins, 2012), observed the requirement of MED13L for the full repression of the cyclin A levels and effective growth suppression and cell cycle arrest (Angus and Nevins, 2012). This finding in fact suggests a role for MED13L in the control of cell proliferation via Rb/E2F pathway, which is not only important in tumorigenesis, but also in the cell cycle-regulated activities of cyclin-dependent kinase 2 during embryonic stem cell differentiation (White et al., 2005).

Utami et al. (2014) have demonstrated improper development of branchyal and pharyngeal arches after morpholino-mediated knockdown of *med13b,* the zebrafish closest orthologue of *MED13L*, due to the defective migration of cranial neural crest cells. Furthermore, their transcriptome analysis of *MED13L*-knockdown neurons derived from human embryonic stem cells revealed differential expression of components of Wnt and FGF signaling pathways (Utami et al., 2014), both crucial for directing neural crest induction (Sauka-Spengler and Bronner-Fraser, 2008; Stuhlmiller and Garcia-Castro, 2012) as well as neurogenesis (Dyer et al., 2014). These findings further support a similar role of MED13L and MED13 in regulation of Wnt target genes (Carrera et al., 2008; Yoda et al., 2005), as well as our previous clinically-based assumption (Asadollahi et al., 2013) of the *MED13L* haploinsufficiency syndrome representing a neurocristopathy.

Overall, the clinical and experimental data indicate an important role for MED13L during embryonic development especially for the regulation of neural crest cells and neurogenesis possibly mainly via the Wnt signaling pathway.

7. Conclusions

MED13L haploinsufficiency syndrome manifests with ID/DD and a recognizable facial gestalt together with additional variable features such as cardiac anomalies (Tables 1 and 2). It appears to be among frequent causes of syndromic ID which should be considered in the differential diagnosis of 22q11.2 and 1p36 deletion as well as Kleefstra syndromes. Nevertheless, descriptions of additional patients with long term follow-up are needed to determine the full course of the disorder. Here, our patient 1 with follow-up into early adulthood in fact provides new information on further development of facial, cognitive and behavioural features in this syndrome. The *de novo* missense mutation in our patient 2 which is identical to the mutation previously reported in a patient with ID and epilepsy (Gilissen et al., 2014), highlights the importance of *de novo* missense mutations as well as potential hotspots along the gene. Yet, the significance of *MED13L* missense variants remains to be determined, since the majority reported so far remain variants of uncertain significance. Regarding the underlying pathomechanisms of the haploinsufficiency syndrome, some evidence suggest the syndrome to be a neurocristopathy (Asadollahi et al., 2013; Utami et al., 2014), but further functional studies are needed for characterizing the molecular pathway.

From the biological standpoint, accumulating evidence suggest that MED13 and MED13L, though both subunits of the multiprotein Mediator complex, can also perform specific functions (Angus and Nevins, 2012; Carrera et al., 2008; Davis et al., 2013; Utami et al., 2014). This is possibly through the relay of information from particular temporal/spatial signals or transcription factors to the RNA polymerase II machinery, thus controlling the expression of specific genes such as those involved in Wnt, FGF and Rb/E2F pathways.

Table 3
Known components (32 components) of the Mediator complex in human and their linked congenital phenotypes/disorders.

Mediator Component	Module	Linked Phenotype/Disorder	References
MED1	Middle	NR	–
MED4	Middle	NR	–
MED6	Head	NR	–
MED7	Middle	NR	–
MED8	Head	NR	–
MED9	Middle	NR	–
MED10	Middle	NR	–
MED11	Head	NR	–
MED12	Kinase	Missense mutations causing Opitz–Kaveggia/FG syndrome, Lujan–Fryns syndrome, and Ohdo syndrome, X-linked disorders characterized by ID and craniofacial dysmorphism and other variable features such as seizure and heart defects, as well as a frameshift mutation causing severe ID and absent language in a family with both male and female patients, as well as missense mutations causing variable ID phenotypes in both male and female patients	[MIM #305450] [MIM #309520] [MIM #300895] (Lesca et al., 2013) (Bouazzi et al., 2015) (Prontera et al., 2016)
MED12L	Kinase	NR	–
MED13	Kinase	An 800 kb heterozygous deletion including *MED13* in a patient with ID, cataract and hearing loss	(Boutry-Kryza et al., 2012)
MED13L	Kinase	Truncating/loss of function copy number variants and mutations causing *MED13L* haploinsufficiency syndrome, as well as missense variants in patients with ID or complex congenital heart defects	[MIM #616789] [MIM #608808] (Table 1)
MED14	Middle	NR	–
MED15	Tail	Deletions of 22q11.2 causing DiGeorge or velocardiofacial syndrome, include *MED15*	[MIM #611867] [MIM #188400] [MIM #192430]
MED16	Tail	NR	–
MED17	Head	A homozygous founder missense mutation in 5 patients with infantile cerebral and cerebellar atrophy, as well as compound missense and splice site mutations in 2 patients with DD, marked choreiform movements with hypotonia, sudden opistotonic posturing and nystagmus	[MIM #613668] (Kaufmann et al., 2010) (Hirabayashi et al., 2016)
MED18	Head	NR	–
MED19	Head/Middle	NR	–
MED20	Head	A homozygous missense mutation in two siblings presenting with infantile-onset spasticity and childhood-onset dystonia, progressive basal ganglia degeneration, and brain atrophy; as well as a *de novo* splice site mutation in a patient with abnormal neurodevelopment and complex congenital heart defects (dextrocardia, partial anomalous pulmonary venous return, mitral atresia, hypoplastic left heart syndrome, aortic atresia)	(Vodopiutz et al., 2015) (Zaidi et al., 2013)
MED21	Middle	NR	–
MED22	Head	NR	–
MED23	Tail	A homozygous missense mutation in a family with non-syndromic ID; as well as compound missense and splice site mutations in 2 brothers of a non-consanguineous family with profound ID, spasticity, congenital heart disease, brain abnormalities, and atypical electroencephalography	[MIM #614249] (Hashimoto et al., 2011) (Trehan et al., 2015)
MED24	Tail	NR	–
MED25	?Tail	A homozygous missense mutation in a family with Charcot–Marie–Tooth neuropathy; as well as compound missense mutations in a patient with Charcot–Marie–Tooth neuropathy; as well as 2 homozygous missense mutations in 2 families with syndromic ID	[MIM #605589] [MIM #616449] (Leal et al., 2009) (Gonzaga-Jauregui et al., 2015) (Basel-Vanagaite et al., 2015) (Figueiredo et al., 2015)
MED26	?Middle	NR	–
MED27	Tail	NR	–
MED28	?Head	NR	–
MED29	Tail	NR	–
MED30	Head	NR	–
MED31	Middle	NR	–
CDK8/19	Kinase	A pericentric inversion in chromosome 6 disrupting CDK19 in a patient with ID, microcephaly, retinal folds and lymphedema	(Mukhopadhyay et al., 2010)
CCNC (cyclin C)	Kinase	NR	–

DD: developmental delay; ID: intellectual disability; NR: not reported.

Conflict of interest

The authors declare no conflicts of interest.

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