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Is MED13L-related intellectual disability a recognizable syndrome?

Short running title: MED13L-related ID

Pernille Mathiesen Tørring¹, Martin Jakob Larsen¹, Charlotte Brasch-Andersen¹, Lotte Nylandsted Krogh¹, Maria Kibæk², Lone Laulund², Niels Illum², Ulrike Dunkhase-Heinl³, Antje Wiesener⁴, Bernt Popp⁵, Giuseppe Marangi⁵, Tina Duelund Hjortshøj⁶, Jakob Ek⁶, Ida Vogel⁷, Naja Becher⁷, Laura Roos⁶, Marcella Zollino⁵, Christina Ringmann Fagerberg¹

¹Department of Clinical Genetics, Odense University Hospital, Odense, Denmark
²Department of Pediatrics, Odense University Hospital, Odense, Denmark
³Department of Pediatrics, Hospital of Southern Jutland, Aabenraa, Denmark
⁴Institute of Human Genetics, University of Erlangen-Nürnberg, Germany
⁵Institute of Genomic Medicine, Catholic University, Hospital A. Gemelli Foundation, Rome, Italy
⁶Department of Clinical Genetics, University Hospital of Copenhagen, Copenhagen, Denmark
⁷Department of Clinical Genetics, and Center for Fetal Diagnostics, Aarhus University Hospital, Aarhus, Denmark

CONFLICT OF INTEREST
All authors declare that they do not have any conflict of interest.

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ABSTRACT
Introduction: MED13L-related intellectual disability is characterized by moderate intellectual disability (ID), speech impairment, and dysmorphic facial features. We present 8 patients with MED13L-related intellectual disability and review the literature for phenotypical and genetic aspects of previously described patients.

Materials and methods: In the search for genetic aberrations in individuals with ID, two of the patients were identified by chromosomal microarray analysis, and five by exome sequencing. One
of the individuals, suspected of MED13L-related intellectual disability, based on clinical features, was identified by Sanger sequencing.

Results: All 8 individuals had de novo MED13L aberrations, including two intragenic microdeletions, two frameshift, three nonsense variants, and one missense variant. Phenotypically, they all had intellectual disability, speech and motor delay, and features of the mouth (open mouth appearance, macroglossia, and/or macrostomia). Two individuals were diagnosed with autism, and one had autistic features. One had complex congenital heart defect, and one had persistent foramen ovale. The literature was reviewed with respect to clinical and dysmorphic features, and genetic aberrations.

Conclusions: Even if most clinical features of MED13L-related intellectual disability are rather non-specific, the syndrome may be suspected in some individuals based on the association of developmental delay, speech impairment, bulbous nasal tip, and macroglossia, macrostomia, or open mouth appearance.

KEYWORDS
MED13L; intellectual disability; developmental delay; MED13L-related intellectual disability; MED13L haploinsufficiency syndrome.

INTRODUCTION
MED13L-related intellectual disability is caused by whole gene deletions or loss of function intragenic variants in the MED13L gene, furthermore several missense variants have been reported. MED13L-related intellectual disability was initially delineated by Asadollahi et al. in 2013 (1) and broadened by further reports (2-4). The syndrome is characterized by moderate intellectual disability (ID), speech impairment, and dysmorphic features, in some cases accompanied by complex congenital heart defects and behavioral issues (1-4). MED13L aberrations were initially believed to be a single-gene cause of complex cyanotic heart disease; however, MED13L-related intellectual disability has been shown to have a broader clinical spectrum, far from always including congenital heart disease (1-4).

A recent review from Asadollahi et al (5) describes MED13L-related intellectual disability to manifest with ID/developmental delay (DD) and a recognizable facial gestalt together with additional variable features, such as cardiac and skeletal anomalies, and autism. Furthermore, Pierre Robin sequence has been reported as a feature of MED13L haploinsufficiency syndrome (6).
Recently, Smol et al. (7) described 36 additional cases and the involvement of missense variants, that seems to cause a more severe phenotype, frequently with epilepsy, and absent ability to speak and walk.

The mediator complex subunit 13-like gene MED13L (MIM 608771) encodes a subunit of the large mediator complex that functions as a transcriptional coactivator for nearly all RNA polymerase II-dependent genes for gene activation or repression (8).

With this report, we describe 8 individuals with likely pathogenic variants in the MED13L gene and conduct a concise review of the current literature to collect standardized phenotypic and genetic information of individuals with MED13L-related intellectual disability. Furthermore, we have submitted this data to public databases to create a snapshot of the current knowledge which will empower further work. We suggest that MED13L-related intellectual disability to some extent is a recognizable phenotype.

MATERIALS AND METHODS

Ethical considerations

Written informed consent to publish clinical data and photographs was obtained for all individuals included in this study.

Individuals

Individual 1 is a boy born at term after 39 weeks of pregnancy, as the only child of healthy, non-consanguineous parents of Polish and Turkish origin respectively. Birth weight was 2558 g (-2SD), length 48 cm (-1SD) and head circumference 32 cm (-2.5SD). At 9 months he was described with hypertonia of extremities, while hypotonia was noted at age 5 years. His developmental milestones were delayed, as he walked few steps with support at 18 months. The greatest concern was very limited eye contact from infancy. Cerebral MRI at age 12 months showed cerebral atrophy. Echocardiography showed a normal structure of the heart. At age 7 years he had severe autism and almost no language. The degree of intellectual disability is difficult to evaluate because of the severe autism but is most likely moderate. Dysmorphic features (Figure 1) were slight epicanthus inversus, long eyelashes, large mouth with a large protruding tongue, low set ears, prominent forehead, and abnormal palmar creases with a Sydney crease at the right hand. He further had hypermetropia (+5/+5.25 D), and strabismus.
Metabolic screening, EEG testing, and genetic testing (FMR1, and karyotype) showed normal results.

**Individual 2** is a boy born at term as the first child of healthy, non-consanguineous Danish parents. Birth weight was 3695 g (+1SD), length 52 cm (+1 SD) and head circumference 35 cm (median to +1SD). His developmental milestones were severely delayed, as at 2.5 years of age he did not crawl and did not say any words. Echocardiography at age 2 showed a patent foramen ovale (PFO), but an otherwise normally structured heart. He had hypermetropia (+3.25/+3.25 D), and alternating esotropia. He had surgery for unilateral cryptorchidism at age 2. Dysmorphic features at age 3 (Figure 1) were brachycephaly, a short neck, slightly low set ears, short up-slanting palpebral fissures, arched eyebrows, broad nasal bridge, malar hypoplasia, full cheeks, a bulbous nasal tip, a large mouth, and a continuous horizontal line at the right hand.

Metabolic screening, and cranial MRI showed normal results as well as genetic analysis (spinal muscular atrophy, FMRI, karyotyping, chromosomal microarray (Agilent 400K oligo array)).

**Individual 3** is a girl born after 41 weeks of pregnancy. She is the second child of healthy, non-consanguineous Danish parents and has a healthy older brother. Birth weight was 3300 g (median), length 51 cm (median) and head circumference 34 cm (median to +1SD). At birth, it was noted that the 5th toe did override the 4th toe of the right foot and that she had a very large tongue. Her developmental milestones were delayed as she crawled at 12 months of age and walked independently at 21 months of age. She had a limited language with only one recognizable word at 24 months.

Dysmorphic features at 24 months (Figure 1) was up-slanting palpebral fissures, broad nasal bridge, a bulbous nasal tip, full cheeks, a large mouth, protrusion of a large tongue, open mouth appearance, retrognatia, camptodactyli of both 3rd fingers, three lateral fingers functions as a unity (claw-like), metatarsus varus of both feet, and 5th toe overlaps the 4th fourth toe of the right foot. Furthermore, lateral deviation of the 2nd toe, and medial deviation of the 3rd and 4th toes was observed. She had feeding difficulties in infancy and has had severe caries in many of her teeth. Echocardiography showed a normally structured heart and hearing and vision were also normal on examination. Based on her clinical features **MED13L** haploinsufficiency syndrome was suspected.
At the age of 3 years her weight was 13 kg (-1SD), length 92 cm (-1SD), and her head circumference was 47 cm (-2 SD). At that time, her vocabulary was limited to ‘yes’ and ‘no’, but she communicated her needs with sign language.

Genetic analysis (EHMT1, RAII, Noonan syndrome gene panel, karyotyping, chromosomal microarray (Affymetrix Cytoscan HD)) showed normal results.

Individual 4 is a girl born at term as the only child of healthy, non-consanguineous parents from former Yugoslavia. Birth weight was 3700 g (+1SD) and length 52 cm (+1SD). In infancy she had a large protruding tongue. Language and motor development have been moderately delayed. She walked independently at 20 months of age. She was diagnosed with autism at age 10 years. At 11 years she was evaluated due to seizures. EEG was abnormal, however, it was concluded that the seizures might be due to vasovagal attacks. As, she did not have additional seizures, no further evaluation was performed.

At the age of 13 years she was still difficult to understand but spoke in sentences. Following dysmorphic features were noted (Figure 1): brachycephaly, low set ears, low nasal bridge, full lips, a large mouth with an open mouth appearance, very narrow ear canals bilaterally, and metatarsus varus of both feet.

Weight was 50 kg (median), height 159 cm (median) and head circumference 54.5 cm (median). Cerebral MRI, Echocardiography, and EKG showed normal results as well as genetic analyses (15q11.2 MLPA, MECP2, FMR1, chromosomal microarray (Affymetrix Cytoscan HD)).

Individual 5 is a boy born after an uneventful pregnancy at 41 weeks gestation as the first child of healthy, non-consanguineous parents of Greek origin. The boy was part of a previous publication, albeit not in detail (ID S_039, Popp et al, 2017 (9)). He was born by Cesarean section, birth weight was 4150 g (+1.5SD), length 53 cm (+1SD), and head circumference 36 cm (+1SD). Motor development was delayed with walking at age 23 months. Speech development was severely delayed with syllable doublings at 15 months and approximately 50 words at 5 years 8 months. As a baby and toddler, he had an open mouth, and a large tongue (Figure 1). Also, he had some feeding difficulties. Besides hypermetropia (+5/+5 D) and strabismus, no organ anomalies were detected.

He attended a school for children with special needs. At 7 years 8 months he was learning first letters, but had no understanding of numbers and quantities. Formal IQ testing at the age of 9 years 2 months resulted in an IQ of 57 (SON-R). He was last reviewed at 11 years 3 months when he had
a height of 134.5 cm (-2SD), a weight of 35.5 kg (-0.5SD) and a head circumference of 53.5 cm (median). Minor morphological aspects included epicanthic folds, strabismus convergens, a flat nasal root, a prominent nasal tip, retrognathia, pes planus and unilateral cryptorchism. Metabolic screening, cranial MRI- and EEG testing showed normal results as well as genetic analyses (karyotyping, FMR1, chromosomal microarray analysis (Affymetrix Genechip 6.0 Array: no pathogenic deletion or duplication (maternally inherited deletion in chr4:30.910.625-31.627.983(hg19); 717 kb, 441 array-markers, no genes)).

**Individual 6** is a boy born at term after an uneventful pregnancy of healthy non-consanguineous Danish parents. Birth weight was 3476 g (median) and length was 53 cm (+1SD). Motor development was delayed with crawling at 1 year and independent walking at 2 years. Speech development was severely retarded, and he was only able to say a few one-syllable words at first visit (4 years 7 month). At follow-up three years later, language development was still severely affected, and he was diagnosed with verbal dyspraxia. There was no reporting of a protruding tongue as an infant, but he liked to suck his tongue.

He attended a school for children with special needs due to learning disabilities and cognitive impairment in moderate degree. Growth parameters were within normal limits. He had surgery for bilaterally cryptorchidism at age one year. He had a Duane anomaly (right eye) and hypermetropia (+4.5 D) and no organ malformations. No specific cardiac evaluation has been performed.

He presented with mild dysmorphic features consisting (Figure 1) of strabismus, down slanting palpebral fissures, large ears, large nose, large mouth, retrognatia and overlapping of the left third toe on the second toe.

Genetic testing (chromosomal microarray (Affymetrix Cytoscan HD), *FMR1*) and metabolic screening were normal. Cerebral MRI showed delayed myelinization at age 3 but was otherwise normal.

**Individual 7** is a boy born prematurely at 32+4 weeks of gestation with a birthweight of 1775g (-4SD), length 44 cm (-3SD) and head circumference 31 cm (-3SD). His parents were healthy. Tetralogy of Fallot was diagnosed prenatally. At birth (Apgar 1/1, 10/10) he was additionally diagnosed with contractures of the hips and thumbs, bilateral metatarsus varus, right sided hydrourether, bilateral inguinal hernia, and left cryptorchism. Necrotic enterocolitis developed shortly after birth. Some feeding problems and intermittent stomach pains have occurred.
sporadically since. Surgery for the heart and hernia was performed within the first year. He is dysmorphic (Figure 1) with open mouth appearance, short bulbous nose, bilateral temporal narrowing, a wide and high forehead, low set ears, small hands and feet with overlapping crooked toes mirrored around 3rd toe. He was later diagnosed with hypermetropia (+5.75/+6.0 D) and is very light sensitive. He has had some delay in motor skills (crawling at 1 year and a walking with support at 2 years), but he has more severe delay in speech development. He spoke 4-5 words at 2 years, but these words have now disappeared at the age of 5. He attends a kindergarten for children with special needs and has autistic features. Growth parameters have stabilized around -2.5SD in length with a head circumference in the normal range.

MR at 15 months showed frontal bilateral alterations in the white matter with lesions and confluence as well as marked periventricular spaces (Figure 1). Genetic testing (chromosomal microarray (Agilent 180k oligo array), Noonan syndrome gene panel, Myotonic dystrophy) and a metabolic screening were normal.

Individual 8 is a boy born after 41 weeks of pregnancy. He is the second child of healthy, non-consanguineous Danish parents and has a healthy older brother and a healthy younger sister. Birth weight 3750 g (median), length 52 cm (median) and head circumference 35 cm (median to +1SD), Apgar 10/1. In the neonatal period, an inguinal hernia was found and surgically corrected. Eye examination revealed bilateral microphthalmia with opacity of the cornea on both sides. On the right side, the pupil was displaced, and on the left side irido-corneal synechiae was found. Retinal function appeared to be normal. During the first two years of life, the corneal opacity decreased, and visual function improved. Dysmorphic features at 24 months was frontal bossing, short palpebral fissures, long eye lashes, broad straight eyebrows and depressed nasal bridge (Figure 1). There was protrusion of the tongue. He has severe neurological abnormalities comprising severe hypotonia, spastic paraparesis, and dystonic movements of the extremities and the tongue. At the current age of 6 years, he can hold his own head, but wears a corset to stabilize the truncus. He cannot sit independently. His oral motor function is impaired, and he is unable to chew and swallow, and has had a feeding tube from the age of one year. Eye contact and smiles can be obtained, but there are no recognizable words.

He has had an MRI twice at the ages of 2 years and 4 years, showing a slightly enlarged ventricular system, partial agenesis of the corpus callosum, and a Dandy-Walker variant.
Echocardiography showed a normally structured heart. At the age of 6 years his weight was 17.2 kg (-2.3SD), length 107 cm (-2.8SD).

Genetic analysis (SOX2, PAX6, B3GALT1, FOXC1, PITX2 and chromosomal microarray (Affymetrix Genechip 6.0 Array)) were all normal.

Clinical features of the eight individuals are described in overview in Table 1.

**Chromosomal microarray analysis**

Chromosomal microarray was performed on DNA isolated from blood samples by Cytoscan HD array (individuals 1,2,3,4, and 6), Genechip 6.0 array (patients 5 and 8), SurePrint G3 180k (Agilent) (patient 7), and Cytoscan 750K (parents) (Affymetrix, Santa Clara, CA, USA) according to the manufacturer’s recommendations. Software used to analyze the data was ChAS (Affymetrix) version 3.1.

**Exome sequencing strategies**

Trio-analysis, exome sequencing:
DNA from individual 2 and individual 8 and their parents was subjected to exome capture using SureSelect Human All Exon V5 (Agilent Technologies) and sequenced on the Illumina HiSeq 2000 platform by Oxford Gene Technology (Oxfordshire, UK). Raw reads were processed using the Burrows-Wheeler Alignment tool (BWA-MEM) v. 0.7.12 (10) and the GATK Best Practice pipeline v. 3.3-0 was used for variant calling (11). Annotation of variants was performed using Annovar (12) for individual 2, and an in-house developed strategy at Department of Human Genetics, Radboud University Medical Center for individual 8. Because both parents were healthy, an X-linked recessive, AR, or de novo AD transmission pattern was possible. Only rare coding variants and splicing variants were considered (minor allele frequency <1%, ExAC database).

DNA from individual 7 and parents were subjected to exome capture using Nimblegene Medexome Plus and sequenced on the Illumina NextSeq 500 platform in the NGS core facility, Department of Molecular Medicine (MOMA), Aarhus University Hospital. Raw reads were processed using BWA-MEM 0.7.15 and GATK v3.6 Best Practice Pipeline. Annotations of variants and genetic inheritance analysis were performed with Ingenuity Variant Analyses. As both parents were healthy, an X-linked recessive, AR, or de novo AD transmission pattern was suspected. Only rare variants were considered (minor allele frequency <0.5%, GnomAD database).
Single exome sequencing:
Exome sequencing was performed on DNA isolated from blood (individual 6) by the Ion AmpliSeq™ exome RDY kit (Life Technologies) for amplification of target regions (>97% of the coding region). Ion Chef was used to prepare libraries which were sequenced using the Ion Proton system (Life Technologies). Base calling, pre-processing of the reads, short read alignment and variant calling was performed using the Torrent Suite including the Torrent Variant Caller (TVC, Version 4.4-5.0) (Life Technology). Variant prioritization was performed with a cascade of filtering steps in VarSeq (Golden Helix). Alamut Visual v.2.8 was used for the annotation and evaluation of missense, nonsense, splice site, and small indels variants.

Exome Pool-Sequencing Method:
The variant in individual 5 was identified in a study where exome sequencing of pooled DNA samples (exome Pool-Seq) was used to screen 96 individuals with sporadic intellectual disability for loss-of-function variants in known ID associated genes from the SysID database (13). Variant validation and segregation analysis was performed by Sanger sequencing followed by genetic fingerprinting using the PowerPlex 21 system (Promega, Fitchburg, WI, USA) to confirm de novo occurrence. This approach is published elsewhere (9).

Direct Sanger sequencing of MED13L (reference NM_015335.4) was performed according to standard procedures (individual 3). The primers are specified in Supplemental Information, Table 3 (SI3). Sanger sequencing was also used to verify variants and evaluate inheritance in some patients and parents.

Review of literature
We searched PubMed April 2018 and identified 21 papers, describing individuals with identified MED13L intragenic and/or copy number variants.

RESULTS
Genotype
Individual 1: Chromosomal microarray analysis revealed a heterozygous de novo deletion of 65 kb, arr[hg19] 12q24.21(116,619,704_116,685,582)x1 dn. The (out of frame) deletion encompassed exon 2 and surrounding parts of introns of the MED13L gene, NM_015335.4: c.(72+1_73-
1)_(310+1_311-1)del, p.(Ala25Leufs*27). The patient is registered in the Decipher database with ID 283932.

Individual 2: Trio exome sequencing revealed a heterozygous de novo nonsense variant (c.2071C>T, p.(Gln691*)) in MED13L (NM_015335.4). One other de novo aberration was detected, a missense variant in KLHL7 (c.1471G>C, p.(Gly491Arg)). KLHL7 has been associated with Retinitis pigmentosa and Cold-induced sweating syndrome. The variant is not described in any public databases and considered likely benign. The MED13L variant was verified using bidirectional Sanger sequencing.

Individual 3: Sanger sequencing of MED13L (NM_015335.4) revealed a heterozygous de novo frameshift variant (c.5861_5890+1del, p.(Glu1954Met fs*15)) in MED13L. The exact consequence of this variant is rather difficult to predict as it might either cause a splicing defect (i.e.: the splice site is not recognized as usual) or a shift in the reading frame (i.e.: the splice site is normally recognized and there is a deletion of 31 nucleotide in the resulting transcript: NP_056150.1:p.(Glu1954Metfs*15)). In both cases loss-of-function would be most likely expected.

Individual 4: Chromosomal microarray analysis revealed a heterozygous de novo 85 kb (out of frame) deletion containing exon 3 and 4 of the MED13L gene, arr[hg19] 12q24.21(116,476,437_116,561,073)x1 dn. NM_015335.4:c.(310+1_311-1)_(479+1_480-1)del, p.(Val105Serfs*31) (registered in the Decipher database, ID 317486).

Individual 5: Exome Pool-Sequencing revealed a heterozygous nonsense variant (c.5173C>T, p.(Gln1725*)) in MED13L (NM_015335.4), which was verified by Sanger sequencing and confirmed to be de novo by Sanger sequencing of the parental samples. Individual 6: Single exome sequencing revealed a heterozygous single base duplication, (c.6274dup, p.(Gln2092Profs*16)) in MED13L (NM_015335.4). The variant was validated by PCR and Sanger sequencing and subsequent sequencing of the parents showed it to be de novo.

Individual 7: Trio exome sequencing revealed a heterozygous de novo nonsense variant (c.5681G>A, p.(Trp1894*)) in MED13L (NM_015335.4). The variant was verified using bidirectional Sanger sequencing.

Individual 8: Trio exome sequencing revealed a heterozygous de novo missense variant (c.3392G>A, p.(Cys1131Tyr)) in MED13L (NM_015335.4). The variant was verified using bidirectional Sanger sequencing.
The seven truncating genetic aberrations detected are considered likely pathogenic causing haploinsufficiency due to nonsense mediated decay. A novel likely pathogenic \textit{de novo} missense variant \textit{p.(Cys1131Tyr)} was identified in individual 8 and absent from gnomAD and ExAC databases. The missense variant is situated in exon 17 and predicted to be ‘probably damaging’ for PolyPhen2 (score 0.998) and deleterious for SIFT (score 0.01). The missense variant leads to the substitution of a strongly conserved nucleotide and amino acid residue in the MED13L gene/protein.

**Phenotype**

The 8 individuals with \textit{MED13L} variants have moderate to severe intellectual disability, and delayed speech and language development. They have common facial features as macroglossia, macrostomia, and/or open mouth appearance, low set ears, upslanting palpebral fissures, bulbous nose, and depressed/broad nasal bridge (Figure 1). Two of our patients have autism spectrum disorder of a severe degree. One had a complex congenital heart defect (Tetralogy of Fallot) and one had persistent foramen ovale (PFO) (Table 1). In addition, the patient, carrying the missense variant, has a very severe phenotype with severe hypotonia, spastic paraparesis, no recognizable words, bilateral microphthalmia, and anterior chamber malformations.

**Review of the literature**

More than 70 patients with definite or suspected \textit{MED13L}-related intellectual disability have been reported so far. In 61 patients, the phenotype was described in detail (1-8, 14-16). Features of these 61 patients and our 8 patients are listed in Table 2, which serve as basis of the review. More detailed clinical information is listed in Supplemental Information Table 1 (SI1). The \textit{MED13L} genetic aberrations identified in the 61 reviewed cases are presented in Figure 2, along with the genetic aberrations in our 8 presented cases.

Patients without description of dysmorphic features and with only limited description of clinical features (17-26), are not included in this review. They are, however, mentioned in Supplemental Information Table 2 (SI2). This group contains \textit{MED13L} variants of unknown significance and inheritance.

In two patients, whole gene duplications of \textit{MED13L} was reported (1, 4), both having a milder degree of ID and speech delay. One of the duplications was maternally inherited. These patients are not included in this review.
DISCUSSION

All 69 reviewed patients had de novo MED13L pathogenic or likely pathogenic variants (Figure 2). Large deletions (whole gene or exons) or large intragenic duplications are identified in 27%, a number most likely overestimated, because chromosomal microarray, by which these cases are identified, is a first line method in diagnostic testing for intellectual disability. Among sequence variants, loss-of-function variants are most frequent (76%). Twelve missense variants considered pathogenic have been reported, including one in our own Individual 8, that had severe hypotonia, spastic paraparesis, no recognizable words at six years, and congenital bilateral microphthalmia. This supports that patients with missense variants seem to frequently have a more severe phenotype with hypotonia, absent speech, and severely delayed motor function, compared to patients with truncating variants (5, 7). Microphthalmia has also been reported in another patient with a missense variant, and in a patient with a splice site variant (7). We agree with Smol et al. (7) and hypothesize that missense variants might induce a dominant negative effect, in contrast to truncating variants. Missense variants in MED13L are reported to cluster in exons 15-17 and 25-31(7), which also holds true for our missense variant which is located in exon 17.

Four additional MED13L missense variants have been reported, but with so limited information regarding phenotype and inheritance that they are not included in this review, nonetheless, they are included in Supplemental Information Table 2 (SI2).

All the reviewed patients have developmental and motor delay (Table 2). Intellectual disability is mostly of moderate degree, but a few patients had mild or severe intellectual disability. Prominent speech delay is present in most patients. Hypotonia is seen in more than half (70%). Abnormalities of hands and feet are described in 45% of the patients, namely club feet, pes cavus deformity, clinodactyly, camptodactyly, overlapping toes, and in one patient limb contractures. Ophthalmological abnormalities are described in 33%, mostly relatively benign findings as strabismus, hypermetropia, hypertelorism, ptosis, and myopia, nonetheless two patients are described with microphthalmia (7) and one patient (Individual 8) with bilateral microphthalmia with clouding of the cornea on both sides, and further, a displaced pupil, and irido-corneal synechiae. Autism or autistic features are reported in 16 of 69 patients (23%), and might be rather severe, as demonstrated by two of our patients.
*MED13L* aberrations were initially believed to be a single-gene cause of complex cyanotic heart disease; however complex heart disease has only been described in 5 of 64 patients (8%) (VSD, tetralogy of Fallot, pulmonary valvular stenosis, and VSD combined with supracardial total anomalous pulmonary venous connection), while 7 of 64 patients (11%) had milder congenital heart defects (6 had persistent foramen ovale (PFO) and one had persistent ductus arteriosus (PDA)).

Common dysmorphic features, seen in at least 50%, are bulbous nasal tip (75%), open mouth appearance (62%), low set ears (52%), and depressed/broad nasal bridge (58%). We find features of the mouth quite characteristic, of these macroglossia seem to be more frequent in infancy and early childhood and may be less evident at older aged. A review of photos from infancy might help suspect the diagnosis. Horizontal eyebrows, which is present in one of our patients, have been a focus in some of the previous papers and are described in 7 of 33 patients (21%).

These common features suggest that *MED13L*-related intellectual disability can be suspected based on clinical features. Nonetheless, due to the extreme genetic heterogeneity of neurodevelopmental disorders and the availability of genome wide screening methods to identify the underlying cause in affected individuals, targeted testing of the *MED13L* gene seems ineffective.

*MED13L* is one of the most commonly mutated genes in neurodevelopmental disorders (27) which is also reflected by the growing number of papers on the subject. Further work is still needed to precisely describe the phenotypic spectrum associated with *MED13L* variants, especially missense variants. Standardized submission of clinical and genetic data to public databases is needed to reach these goals in the future.

**CONCLUSION**

The majority of *MED13L* aberrations are identified by chromosomal microarray analysis and exome sequencing, the syndrome being composed of somewhat unspecific symptoms. We suggest, however, that *MED13L*-related intellectual disability might be recognizable in patients with moderate ID, severe language delay, bulbous nasal tip, and features of the mouth/tongue as macroglossia (perhaps only evident at early age), macrostomia, and/or open mouth appearance. However, even if *MED13L*-related intellectual disability is clinically recognizable, the improved access to genome-wide analysis makes single gene analysis less attractive.
REFERENCES


Table 1. Clinical and dysmorphic features of individuals 1-8 reported in this study

Abbreviations: NA, not available; DD, developmental delay; F, female; M, male.

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**MED13L (NM_015335.4) variants (all de novo)**

- Exon 2 deletion, c.2071C>T, p.Gln691*
- Exon 3 deletion, c.5861_5890+1del, p.Glu1954Metfs*15
Table 2. Clinical features of 69 individuals (35 female, 34 male) with likely pathogenic *MED13L* variants

The table presents an overview of 69 individuals with likely pathogenic *MED13L* variants (61 published cases and our 8 cases. For additional description, please see Supplemental Information Table 1 (SI1). Abbreviations: PFO, persistent foramen ovale; PDA, persistent ductus arteriosus.

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<th></th>
<th>No of patients</th>
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<td>Intellectual disability</td>
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<tr>
<td>Motor delay</td>
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<td>100%</td>
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<tr>
<td>Speech delay</td>
<td>68/69</td>
<td>99%</td>
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<td>Anomalies of hands and/or feet</td>
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<td>45%</td>
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<td>Hypotonia</td>
<td>46/66</td>
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<tr>
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<td>12/64 - 5/12</td>
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<td>- PFO/PDA</td>
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<td>Autistic features</td>
<td>16/69</td>
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**Dysmorphic features**

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<thead>
<tr>
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<tr>
<td>Bulbous nasal tip</td>
<td>50/67</td>
<td>75%</td>
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<tr>
<td>Open mouth appearance</td>
<td>40/65</td>
<td>62%</td>
</tr>
<tr>
<td>Depressed/broad nasal bridge</td>
<td>19/33</td>
<td>58%</td>
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<tr>
<td>Low set ears</td>
<td>17/33</td>
<td>52%</td>
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<tr>
<td>Macrostomia</td>
<td>14/33</td>
<td>42%</td>
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<tr>
<td>Upslanting palpebral fissures</td>
<td>26/65</td>
<td>40%</td>
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<tr>
<td>Macroglossia</td>
<td>9/33</td>
<td>27%</td>
</tr>
<tr>
<td>Bitemporal narrowing</td>
<td>8/33</td>
<td>24%</td>
</tr>
<tr>
<td>Brachycephaly</td>
<td>7/33</td>
<td>21%</td>
</tr>
<tr>
<td>Horizontal eyebrows</td>
<td>7/33</td>
<td>21%</td>
</tr>
<tr>
<td>Large ears</td>
<td>6/33</td>
<td>18%</td>
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</tbody>
</table>
LEGENDS

Figure 1. Photos of individuals 1-8 reported in this study
Numbering on the photos refer to the number of the 1 (4) infancy and 13 years; (5) 12 months; (6) 7 years old (7) infancy and 4 years; (8) 2 years old. Bulbous nasal tip, protruding tongue, macrostomia, and/or open mouth appearance are seen in most patients. The feet of individuals 3, 6, and 7 are seen with overlapping toes. Note severe hypotonia in individual 8 with a missense variant.

Figure 2. Diagrammatic presentation of MEDI3L (NM_015335.4) with exons 1–31 (not drawn to scale).
MEDI3L aberrations identified in our cases are highlighted in bold print, and previously published aberrations are indicated in normal print. Numbers for references refer to the general reference list of the paper. A. Truncating variants are represented above the gene and missense variants under the gene. B. Location of intragenic deletions and duplications, along with one larger whole-gene deletion, indicated by horizontal bars.

Supplemental Information: Table 1 (SI1), Table 2 (SI2) and Table 3 (SI3)
SI1: Detailed information of phenotype and genotype of the patients included in this review.
SI2: The patients suspected of MEDI3L-related intellectual disability, which were excluded of this review.
SI3: List of the PCR primers used in MEDI3L Sanger sequencing.