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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