CLINICAL REPORT

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Intellectual disability associated with craniofacial dysmorphism, cleft palate, and congenital heart defect due to a de novo *MEIS2* mutation: A clinical longitudinal study

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Abstract

Intellectual disability (ID) has an estimated prevalence of 1.5%–2%. Whole exome sequencing (WES) studies have identified a multitude of novel causative gene defects and have shown that sporadic ID cases result from de novo mutations in genes associated with ID. Here, we report on a 10-year-old girl, who has been regularly presented in our neuropediatric and genetic outpatient clinic. A median cleft palate and a heart defect were surgically corrected in infancy. Apart from ID, she has behavioral anomalies, muscular hypotonia, scoliosis, and hypermobile joints. The facial phenotype is characterized by arched eyebrows, mildly upslanting long palpebral fissures, prominent nasal tip, and large, protruding ears. Trio WES revealed a de novo missense variant in *MEIS2* (c.998G>A; p.Arg333Lys). Haploinsufficiency of *MEIS2* had been discussed as the most likely mechanism of the microdeletion 5q14-associated complex phenotype with ID, cleft palate, and heart defect. Recently, four studies including in total 17 individuals with intragenic *MEIS2* variants were reported. Here we present the evolution of the clinical phenotype and compare with the data of known individuals.

KEYWORDS
cardiac septum defect, cleft palate, craniofacial dysmorphism, intellectual disability, *MEIS2*

1 | INTRODUCTION

Intellectual disability (ID) has an estimated prevalence of 1.5%–2% (Leonard & Wen, 2002). Whole exome sequencing (WES) studies have identified a multitude of novel causative genetic variants and have shown that a large proportion of sporadic ID cases in fact result from de novo mutations with a constantly growing number of newly discovered genes (Leonard & Wen, 2002).

In 2007, Erdogan and coworkers linked a patient presenting with atrial septal defect type secundum (ASD II), cleft palate, moderate developmental delay, severe speech delay, and mild motor delay to a 5.3 Mb deletion in 15q14 (Erdogan et al., 2007). In 2008 and 2010,

two further patients with cleft palate and ventricle septal defect (VSD) were identified, showing a deletion of 5.6 Mb and of 123 kb in 15q14, respectively (Chen et al., 2008; Crowley et al., 2010).

Notably, the only gene affected in all patients was *MEIS2*, strongly indicating that heterozygous loss of *MEIS2* as cause for the clinical manifestation of cleft palate, cardiac septal defects, and varying degrees of developmental delay. In 2014, Johansson and colleagues added nine more patients with *MEIS2* mutations (five deletions and four duplications) to the growing list of cases, validating the clinical spectrum with clefting (7/9), ventricular septal defects (3/9), delayed motor development, and learning disability (9/9), but not showing consistent facial dysmorphisms (Johansson et al., 2014). Shortly after, a one nucleotide deletion (c.998_1000del; p.Arg333del) within *MEIS2* was published, identified in a girl with cleft palate, congenital heart defect and further associated findings including feeding problems, facial dysmorphism, severely delayed development and autism spectrum disorder (Louw et al., 2015) supporting the concept of *MEIS2* as a gene causative for this complex phenotype. Three further independent individuals with *MEIS2* variants were reported—a girl with severe ID, cleft palate, cardiac septal defect, and severe feeding difficulties (c.611C>G, p.Ser204*) (Fujita et al., 2016); a girl with clinical diagnosis of Rett syndrome but negative *MECP2* analysis (c.955A>G, p.Arg319Gly) (Srivastava et al., 2018); and a patient with ID, absent speech, epilepsy, facial dysmorphism, larynx malposition, and congenital heart defect diagnosed with a balanced chromosomal rearrangement [t(11;15)([p14;q14)] causing a disruption of *MEIS2* (Schluth-Bolard et al., 2019). Recently, four studies were published including in total 17 individuals with pathogenic variants leading to haploinsufficiency of *MEIS2*. Remarkably, *MEIS2* haploinsufficiency has been discussed as the most likely mechanism of the microdeletion 15q14-associated complex phenotype with ID, cleft palate, and heart defect (Douglas et al., 2018; Giliberti et al., 2020; Hildebrand et al., 2020; Verheije et al., 2019), thus adding *MEIS2* to the growing number of genes underlying syndromal ID. However, until now, no studies presenting longitudinal data of the evolving phenotype have been published.

2 | CLINICAL REPORT

The patient described in this report is the second born child of healthy, unrelated parents of Caucasian descent. Family history was unremarkable (the 4 years older sister is healthy and normally developed). The patient was clinically investigated over a decade:

2.1 | 0–4 weeks (newborn)

Pregnancy was uneventful and spontaneous delivery was at term with normal birth measurements. Postnatally, the patient developed a newborn sepsis due to beta-hemolytic streptococci, no further information available.

2.2 | 1–12 months of age (infant)

A median cleft palate was supplied with a plate and adjusted regularly. Due to feeding difficulties (problems to suck and to swallow) and resulting dystrophy (−2.5z at the age of 4 months), the infant formula ("Pre-nutrition") was enriched with rapeseed oil. A VSD and an ASD were surgically corrected at 12 months of age.

2.3 | 1–2 years of age (toddler)

The patient developed tracheomalacia (including stenosis of left main bronchus) causing recurrent pulmonary infections. The median cleft palate was surgically corrected at 1 $^{5/12}$ years of age. Her psychomotor development was significantly delayed (sitting independently with 21 months, crawling with 24 months) and was confirmed by assessment of motor, speech, and cognitive development ("Münchener Funktionelle Entwicklungsdiagnostik" [MFED]) at 2 $^{6/12}$ years. Due to the severe developmental delay noted in the MFED, Bayley-Scales of Infant Development II were performed complementary at 2 $^{11/12}$ years of age and showed a cognitive-verbal developmental age of 13 months and motor developmental age of 10 months. Facial dysmorphism included protruding ears and thin arched eyebrows (Figure 1(a)).

2.4 | 3–5 years of age (pre-schooler)

Feeding problems and dystrophy persisted (−2.9z at the age of 3.5 years). Motor and speech development remained severely delayed, but a slow developmental progress was reported by the parents. Independent walking was achieved at 4 years and first words were spoken at 5 years. At the age of 5.5 years, a further Bayley-Scales of Infant Development II was performed (SON-R was not possible to be performed) revealing a delay of minimum 3.5 years (cognitive-verbal developmental age of 22 months, motor developmental age of 18 months). Apart from ID, behavioral problems such as (auto-)aggression and lack of distance were noticed. The large protruding ears and thin arched eyebrows appeared more evident (Figure 1(b)).

2.5 | 6–10 years of age (school-aged child)

The patient was externally diagnosed with infantile autism using the ADI-R (diagnostic interview for autism) and the ADOS-G (standardized observation scale for autistic disorders). Her increasingly aggressive behavior required a medication with risperidone since the age of 7 years. Toilet training and threat awareness were not age-appropriate. She was only able to speak few words and some simple 2–3-word sentences. Another MFED performed at 9 $^{10/12}$ revealed an overall developmental age of 34 months. Her posture was dominated by muscular hypotonia, hypermobile joints, and a mild right convex thoracic scoliosis (Figure 1(f), (g)) with a Cobb angle of 22° (Figure 1(h)) requiring a gummed brace. Her facial dysmorphisms became more evident over time,
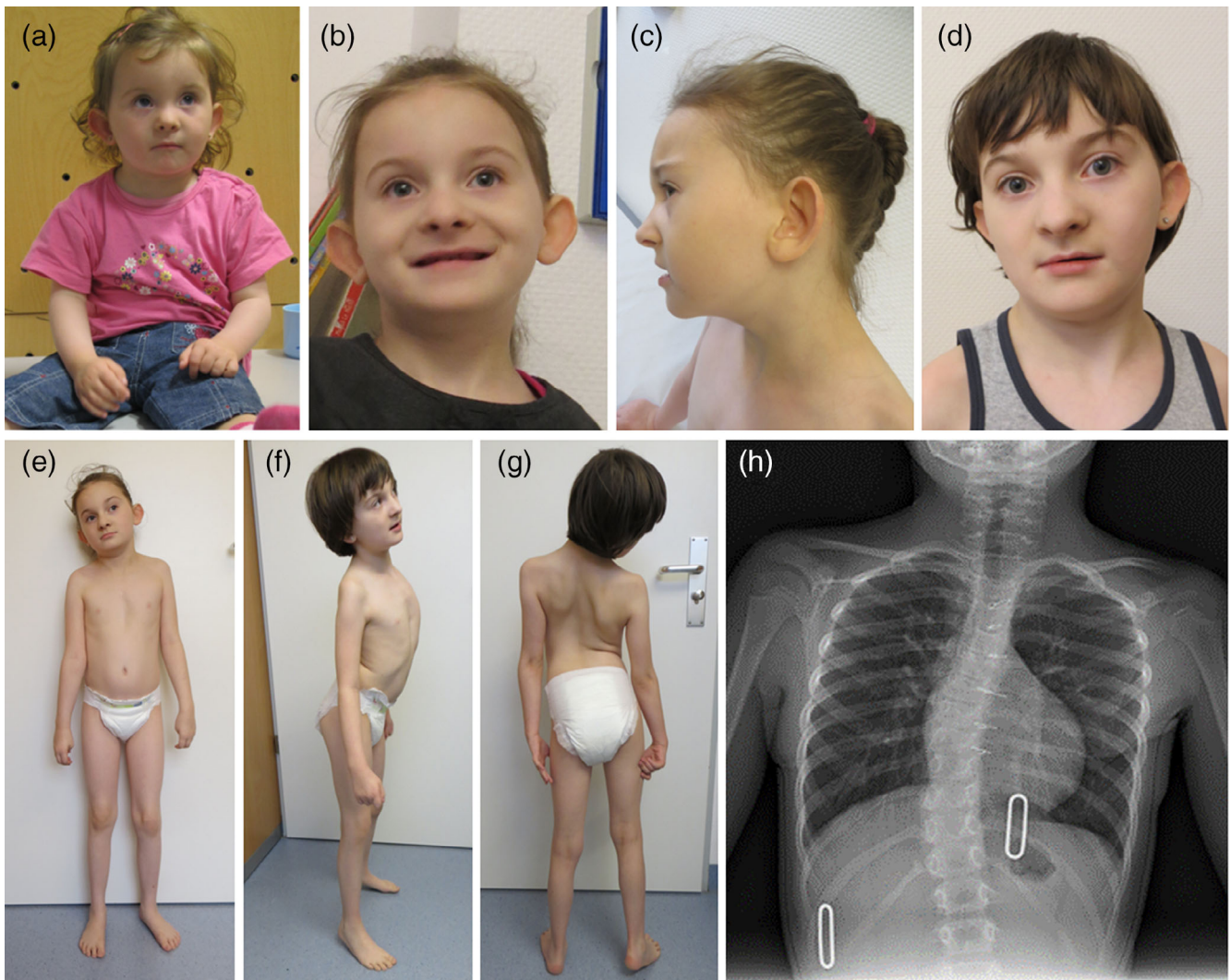
FIGURE 1 Clinical presentation of our *MEIS2* patient: (a) At age of 2 $^{5/12}$ years with large protruding ears and thin arched eyebrows. (b) At the age of 6 $^{6/12}$ and (c, e) 8 $^{7/12}$ years with more distinctive facial dysmorphism and muscle hypotonia. (d, f, g) At the age of 9 $^{10/12}$ years facial features, such as thin and arched eyebrows, thin lip vermillion and prominent nasal tip with short alae nasi, and large, protruding ears with enlarged fossa triangularis and hypoplastic antihelix, are evident. (f, g) In addition to the evolving facial phenotype and muscle hypotonia, the patient developed hypermobile joints and scoliosis. (h) Standing/sitting x-ray of the thorax showing a right convex thoracic scoliosis with Cobb angle of 22° and mild rotation component [Color figure can be viewed at wileyonlinelibrary.com]

characterized by thin and arched eyebrows, thin lip vermillion and prominent nasal tip with short alae nasi, and large, protruding ears with enlarged fossa triangularis and hypoplastic antihelix (Figure 1(a)–(f)). Growth parameters at 9 $^{10/12}$ years of age were weight 23.4 kg (2nd percentile, −2.12z); height 125.9 cm (1st percentile, −2.19z); head circumference 50 cm (1st percentile, −1.9z); BMI 14.8 kg/m^2 (15th percentile, −1.05z). For the course of growth parameters see Figure 2.

3 | MATERIALS AND METHODS

### 3.1 | Editorial policies and ethical considerations

All data concerning our patient was extracted from her medical routine files. This approach was approved by our local ethics committee.

For all diagnostic steps, written informed consent was obtained from both parents. The permission to publish clinical data and photos was obtained from her father (now sole custodian). The study was conducted in accordance with the principles of the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

3.2 | Genetic analyses

First, regular karyotyping followed by microarray analysis were performed. As the girl's clinical and phenotypic features showed some overlap with those present in Kabuki's syndrome (ID, congenital heart defects, low measurements, facial phenotype with high arched eyebrows and ear deformities), analyses of *KMT2D* and *KDM6A* were
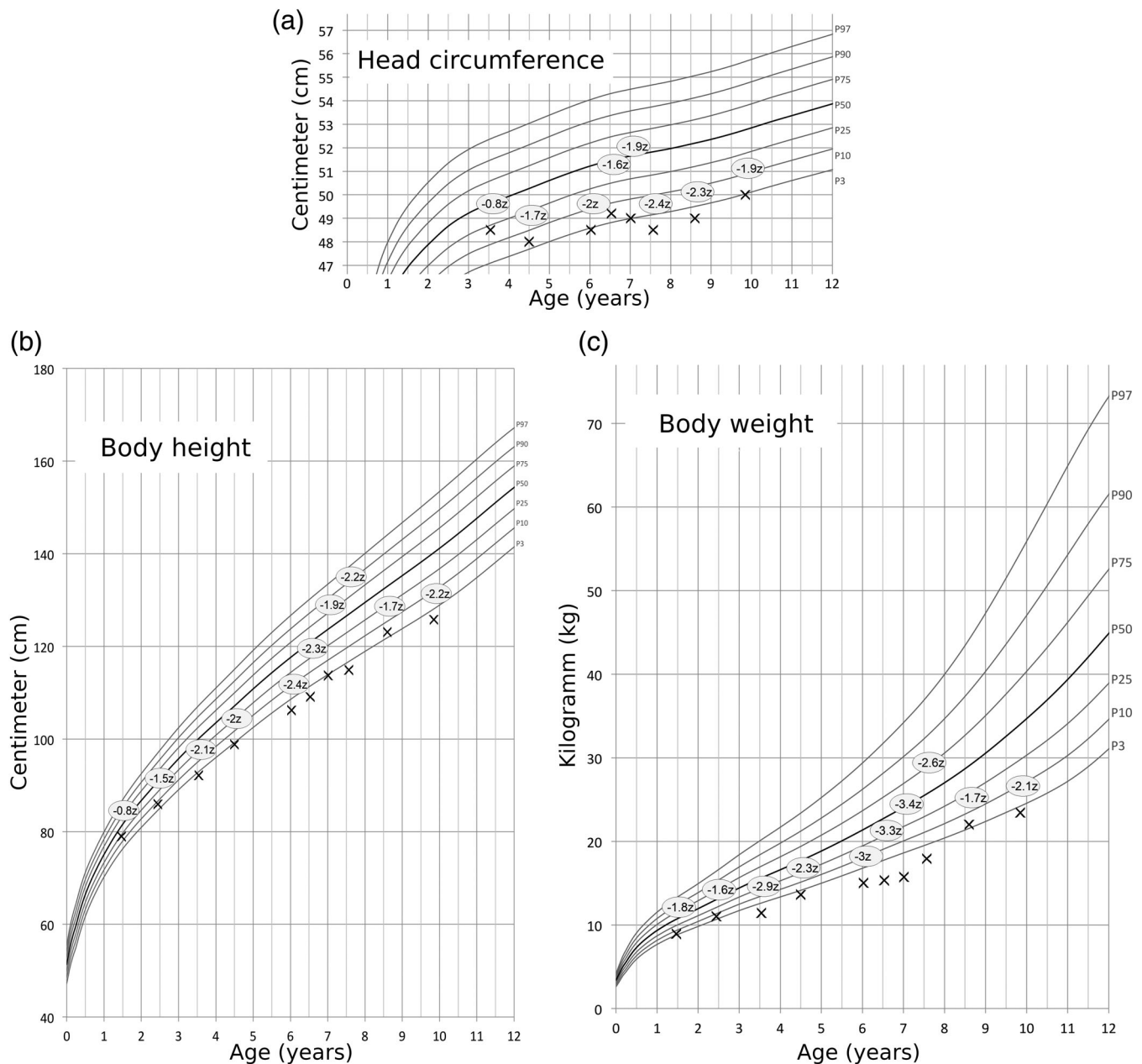
FIGURE 2 Course of growth parameters: (a) head circumference, (b) body height, (c) body weight. Standard deviations of each measurement indicated as *z*-score. Percentiles from: Referenzperzentile für anthropometrische Maßzahlen und Blutdruck aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KIGGS), Robert-Koch-Institut 2013, 2. Auflage, ISBN 978-3-89606-218-5. Created with: Ped(z)-Kinderarztrechner (www.pedz.de)

carried out as a second step. Third, trio analysis by exome analysis was conducted. For variant analysis CCG varbank (https://varbank.ccg.uni-koeln.de/) was used. For confirmation, polymerase chain reaction (PCR) and Sanger sequencing of exon 10 including flanking intron sequences of *MEIS2* gene (OMIM 601740) were performed.

4 | RESULTS

Regular karyotyping was normal. Microarray analysis showed a partial deletion in *ITPR2*, which was further defined as inherited benign

familial variant. Molecular genetic analyses of *KMT2D* and *KDM6A* showed no pathological findings, making Kabuki syndrome (MIM #147920 and #300867) unlikely. Trio exome sequencing revealed a heterozygous de novo missense variant (c.998G>A, p.Arg333Lys; RefSeq NM_170674.4) in *MEIS2* (MIM *601740) located on chromosome 15q14. Subsequent Sanger sequencing of exon 10 of *MEIS2* gene confirmed the findings of exome analysis. This variant was predicted in silico to be damaging/deleterious/disease causing (PolyPhen2/SIFT/Mutation Taster) with a CADD score of 28.7 and was absent in the GnomAD database (http://gnomad.broadinstitute.org/).

5 | DISCUSSION

Here, we report the seventh patient with a missense mutation in *MEIS2* leading to syndromic ID associated with craniofacial dysmorphism, cleft palate, and congenital heart defect. One patient with the identical missense variant (c.998G>A, p.Arg333Lys) was described only very recently by Verheije et al. (2019). This patient presented with ASD and VSD, profound developmental delay, and facial dysmorphism but also additional duodenal stenosis, hypothyroidism, transitory pancreatitis, nephrocalcinosis, bilateral inguinal hernia, stenosis of the left lower pulmonary vein, and persisting respiratory insufficiency leading to tracheotomy at the age of 11 months and his early death at the age of 13 months. Due to the patient's severe phenotype and atypical features, a multilocal genomic variation was assumed. Indeed, exome sequencing of this patient also revealed a de novo intragenic 185-bp deletion of *FOXP1* and compound heterozygosity for rare variants in the *LRP2* gene (Verheije et al., 2019). This complex genotype might explain the differences in genotype–phenotype correlation of our patient in comparison to the patient described by Verheije et al. (2019). Moreover, comparison of clinical features and genetic findings of these two cases emphasizes the relevance of combining and considering all patient data to describe unambiguous phenotypes enabling a "clinical refinement" as provided by our case for the first time for pathogenic *MEIS2* missense variants.

Pulmonary symptoms as described in our patient with severe tracheomalacia including stenosis of left main bronchus causing multiple pulmonary infections are so far not described as typical for patients with *MEIS2* mutations. However, in two further *MEIS2* patients similar findings were observed before: one female patient described by Louw and colleagues in 2015 with a small de novo in-frame deletion (c.998_1000del; p.Arg333del) affecting the same amino acid as in our patient, showed congenital lobar emphysema of the left upper lobe (Louw et al., 2015). In 2019, Verheije and colleagues described in the already above-mentioned patient persisting pulmonary insufficiency leading to tracheotomy at the age of 11 months and early death at the age of 13 months.

As shown in Figure 1, the "*MEIS2* phenotype" evolves and becomes more evident over time. Up to now, 49 patients carrying pathogenic *MEIS2* variants were described in literature (Giliberti et al., 2020; Hildebrand et al., 2020). Our case is the seventh patient presenting with a pathogenic *MEIS2* missense variant. Comparison with the one individual known to carry the identical *MEIS2* missense mutation but also additional sequence variants allows a clinical refinement which supports the concept that pulmonary problems might be (a less frequent) feature of this syndromic *MEIS2* phenotype.

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