Autosomal recessive otospondylo-mega-epiphyseal dysplasia: comprehensive clinical review of a pediatric cohort

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Autosomal recessive otospondylo-mega-epiphyseal dysplasia (OSMEDB) is characterized by short stature with short limbs, dysmorphic facial features, and hearing loss, which is caused by biallelic, loss-of-function, variants in the *COL11A2* gene. Geno-phenotypic data from the medical records of eight affected individuals from five unrelated families was abstracted, recorded in an Excel spreadsheet and analyzed using simple frequency analysis. Either short femora or short extremities with or without other ultrasonographic abnormalities were demonstrated in five patients antenatally. The mean height was -2.29 SDS. Pectus deformity, including either chest asymmetry or pectus excavatum, was present in five patients. Bilateral hearing loss was verified in all patients. Severe speech delay and learning disabilities were present in two patients whose deafness was realized after the age of 12 months. Four novel loss-of-function variants in *COL11A2* were found in this cohort. We present novel geno-phenotypic findings in a pediatric cohort with OSMEDB. The age of manifestation of short stature was variable, ranging from birth to middle childhood, and the severity of short stature varied even within the same family. Hearing loss may not be evident in the neonatal period and manifest later in OSMEDB. Intermittent hearing tests should be performed for early intervention of neurolinguistic delay and learning disabilities. *Clin Dysmorphol* 32: 151–155

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Introduction

Otospondylo-mega-epiphyseal dysplasia (OSMEDB) is a rare skeletal dysplasia, classified in Type11 collagenopathies, characterized by both autosomal dominant and recessive inheritance patterns (Mortier *et al*., 2019). Vikkula *et al*. have identified homozygosity for a missense variant in the *COL11A2* gene as the cause of the disorder in three affected sibs in a Dutch family for the first time (Vikkula *et al*., 1995). Pihlajamaa *et al*. proposed that OSMED occurs in both autosomal dominant (OSMEDA; # 184840) and autosomal recessive (OSMEDB; #215150) forms due to heterozygous or homozygous mutations, respectively, in the *COL11A2* gene (Pihlajamaa *et al*., 1998).

Biallelic loss of function mutations of the *COL11A2* gene has been associated with OSMEDB, Fibrochondrogenesis 2, and non-syndromic autosomal recessive hearing loss phenotype. A specific type of hot spot region or variant localized in *COL11A2* has not been linked specifically to the OSMEDB phenotype. However, the majority of the previously reported variants are either frameshift or nonsense variants that result in functionally null allele secondary to protein truncation or nonsense mRNA decay (Chen *et al*., 2005).

OSMEDB can be distinguished clinically from the autosomal dominant form based on the basis of typical facial features, including midface hypoplasia with a short upturned nose and significantly depressed nasal bridge, disproportionate short stature with short extremities, enlarged thick epiphyses and abnormalities of the vertebral bodies and non-progressive, sensorineural hearing loss (Temtamy *et al*., 2006). The prevalence is unknown but less than 30 cases have been described in the literature so far (https://www.orpha.net/). Here, we present eight cases from five unrelated families with one recurrent and four novel pathogenic *COL11A2* homozygous variants to elaborate on the distinct clinical and radiologic features of the OSMEDB.

Materials and methods

The collection of the clinical data

The hospital records of eight patients from three tertiary reference centers were evaluated retrospectively. Informed consent was obtained from families for publishing the photographs and clinical data of their children. Only patients whose diagnoses were confirmed by genetic analysis were included in the study. The patients' age at admission, gender, prenatal and postnatal histories, anthropometric measurements, craniofacial and other clinical features of the patients, and the results of the genetic analysis were noted. To emphasize the demonstrative facial features of patients in different age ranges, the facial photographs taken from the front and

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sides were also included in the study. The X-rays of the patients obtained at various ages were also reevaluated. Transient Otoacoustic Emissions, Distortion Product Otoacoustic Emissions, Automated and Clinical Auditory Brainstem Response (AABR and ABR) measurements, were performed for audiological evaluation as recommended by the National Institutes of Health Consensus Development Conference in 1993 for Universal hearing screening (Morton and Nance, 2006)

Molecular analysis

Genetic analysis of families I, II and III were carried out using the method of Sanger sequencing. Exons 30–66 were screened for variations in the *COL11A2* gene with conformation-sensitive gel electrophoresis (CSGE). PCR product of each exon was mixed with an equal amount of PCR product from a healthy control subject before heteroduplexing. PCR products with heteroduplexes in the CSGE analysis were then sequenced with ABI PRISM 3100 sequencer and Big Dye Terminator Sequencing Kit (Applied Biosystems) to define the underlying sequence variations. The parents of the patients were analyzed simultaneously. All the coding exons and the intronic–exonic boundary regions of the *COL11A2* gene were sequenced by the NGS method (Miseq-Illumina) for families IV, V, and VI. The design target coverage was 99.49%. A minimum of 30X coverage for all bases was accepted for a reliable variant calling. The segregation analysis was performed for all families.

Results

Clinical findings

Four female and four male patients from five unrelated families were enrolled in the study. The youngest patient was 5 months old and the oldest one was 13 years old. All families included consanguineous couples (first cousin parents), and there was more than one affected family member in two families (FIII, FIV).

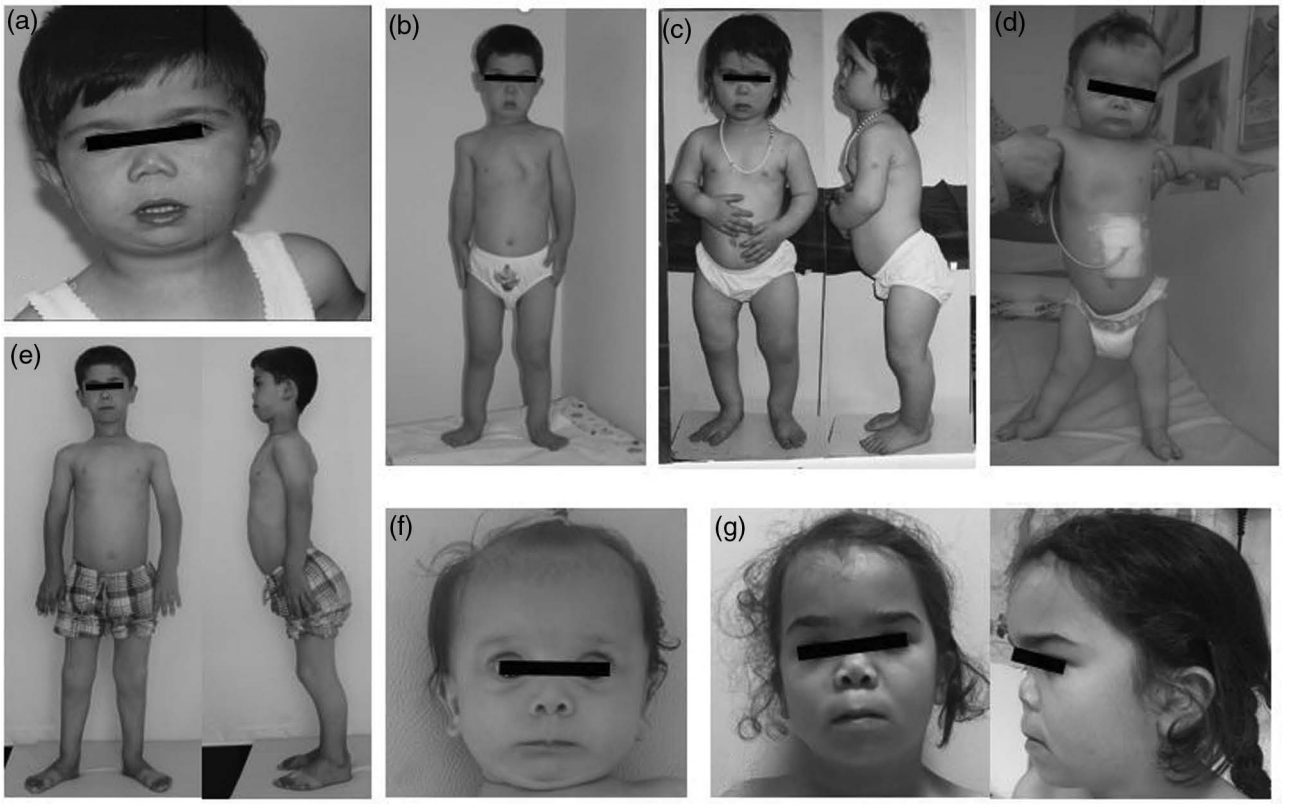
Antenatal evaluation results were available in 5 of 8 patients. Short femura or short extremities were detected in all these patients (5/5) antenatally (Table 1). One of these patients had polyhydramnios (P1) and one patient (P6) had nonimmune hydrops as accompanying findings in antenatal ultrasound. Four of the patients (4/8) were born on term, while three patients were late preterm (one was born on the 34th gestation weeks and two were 36th gestation weeks). Birth weight was noted in five patients and, birth height was known only in two patients. Birth weight and height percentiles of the patients were calculated according to their gestational ages (Kurtoglu et al., 2012). The minimum birth weight was 2200 gr (50th P) at 34th weeks (P5), and the maximum birth weight was 4000 g (97th P<) at 36th weeks (P6). The heights of P7 and P8 at birth were at the lower limit for gestational age but not below the 3rd percentile.

Table 1 **The summary of the main clinical features of the patients**

F	P	Age	Gender	Antenatal findings	GA	Growth parameters					Hearing loss	Cleft palate	Common facial features[a]	Pectus deformity
						Birth		Current						
						Height (cm)	Weight (g)	Height (cm)	Weight (kg)	OFD (cm)				
I	1	3 yr	F	Polyhydramnios, short femur	Term	NA	NA	91 (13.57P) (−1.1SD)	12.3 (12.51P) (−1.15 SD)	47 (12.92P) (−1.13SD)	SN	-	+	-
II	2	4 yr	M	NA	Term	NA	NA	97.7 (6.94P) (−48SD)	15.8 (31.92P) (−0.47SD)	49.5 (14.92P) (−1.04SD)	SN	+	+	+
III	3	3 yr	F	Short limbs	Term	NA	4015 (>90P)	92 (19.77P) (0.85SD	16.5 (89.62P) (1.26SD)	49.5 (70.19P) (0.53SD)	SN	-	+	-
	4	13 mo	M	NA	NA	NA	NA	74 (11.12P) (1.22SD	8.7 (7.78P) (−1.42SD)	52 (99.93P) (3.18SD)	Mx	+	+	+
	5	7.5 yr	M	NA	34 w	NA	2200 (50–75P)	102 (<0.02) (−24SD)	22.6 (39.74P) (−0.26SD)	52 (44.43SD) (−0.14SD)	SN	-	+	+
IV	6	10 yr	M	Nonimmune hydrops, short limbs	36 w	NA	4000 (>90P)	117 (0.03P) (3.48SD)	25 (6.55P) (−1.51SD)	49 (0.09P) (−3.12SD)	SN	+	+	-
	7	5 mo	F	Short limbs	36 w	43 (10–25P)	2600 (50P)	54 (0.82P) (−72SD)	3.9 (0.33P) (−2.72SD)	35 (< 0.02P) (−4.03SD)	SN	+	+	+
V	8	13 yr	F	Short limbs	38 w	45 (25P)	3600 (50P)	132 (0.06P) (−3.26SD)	36 (6.3P) (−1.53SD)	51 (0.24P) (−2.82SD)	SN	-	+	+

F, family; GA, gestational age; Mx, Mix; NA, not available; OFD, occipitofrontal diameter; P, patient; P, percentile; SN, sensorineural.
[a]Severe depressed nasal root, short nose, midface hypoplasia, micrognathia.

Fig. 1



Demonstration of some dysmorphic features of patients on some selected photographs. (a, f, and g) (patients 1, 7 and 8): Severely depressed nasal root, extremely short nose with anteverted nostrils; (b and d) (patients 2 and 4): Pectus deformity; (c and e) (patients 3 and 7): Short extremities, especially apparent on the upper, lumbal lordosis.

Growth measurements of the patients were calculated according to Turkish children's growth charts (Neyzi *et al.*, 2015). The mean weight score by age at the first visit was −0.97 SDS (min: −2.72; max: +1.26), mean height: −2.29 SDS (min: −4.24; max: −0.85), and mean occipitofrontal circumference: −1.07 SDS (min: −4.03; max: 3.18). Weekly recombinant human growth hormone therapy was initiated in only P6 with the suggestion of pediatric endocrinology for 2 years due to having low growth velocity (below 4 cm/year). His height velocity was 6 cm/year during the last visit.

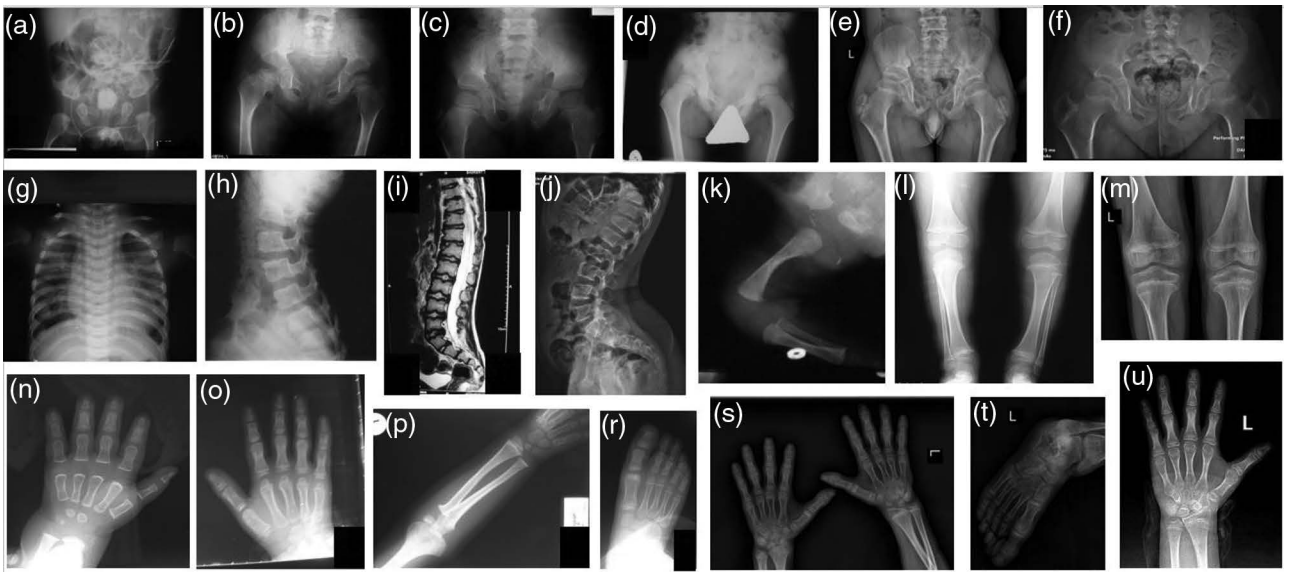
Figure 1 includes the consented photographs of the affected individuals. All (8/8) present with midface hypoplasia, severe nasal rooth depression with a small nose and micrognathia, whereas only four of them had a posterior cleft palate (4/8). The diagnosis of bilateral sensorineural hearing loss was verified in 7 of 8 patients, whereas one (P4) had mix-type hearing loss. One patient (P7) failed in neonatal hearing screening. There were severe speech delays and learning disabilities in two patients (P5, P6) who realized hearing loss after the 12th month. The other three patients had moderate speech delay without learning disabilities and started to use hearing aid before the 12th month. One patient (P8), whose cochlear implant was placed in after the age of one, had a noneurolinguistic delay. Gross motor developmental delays were also noted in P4 and P6.

All the patients had short extremities. Some of them also had short hands. Common radiologic findings included short long bones, enlarged epiphyses, broad metaphyses, squared pelvis, and mild to moderate platyspondyly (Fig. 2). Pectus deformity, including either chest asymmetry or pectus excavatum, was present in five patients. P6 was operated on for a restricted flexion range of motion of his knees at the age of 2 years.

Molecular findings

The *COL11A2* variants were described using the Human Genome Variation Society nomenclature guidelines and checked against those available in 1000 Genomes, dbSNP, ClinVar, and Human Genome Mutation Database. American College of Medical Genetics and Genomics Standards and Guidelines were used for the determination of variant pathogenicity (Richards *et al.*, 2015) The previously reported homozygous nonsense variant was identified in P1. However, three novel homozygous frameshift variants and one novel homozygous nonsense variant were described in other patients (Table 2).

Fig. 2



Radiologic imaging of the patients at several ages. (a) 13 months (patient 4): The lower ilia and, femoral heads are broad; (b) 3 years (patient 1), (c) 3 years (patient 3), and (d) 4 years (patient 2): The proximal femoral epiphyses are large; (e) 10 years (patient 6) and (f) 13 years (patient 8): The proximal femora are wide and the necks are in the valgus position; (g) 13 months (patient 4): Sligthly widening of the ribs; (h) 3 years (patient 1): Dysregularities on the upper and lower palate of the vertebral bodies; (i) 4 years (patient 2): Double hump appearence on the vertebral corpus; (j) 13 years (patient 8): Platyspondyly especially appearent on thoracicvertebra and increased lumbal lordosis; (k) 13 months (patient 4): Short tubular bones, dumble shape femora; (l) 3 years (patient 3), 13 years (patient 8): The femoral and tibial epiphyses are large; (n) 13 months (patient 4) and (o) 3 years (patient 3): Dumble shape middle phalanx; (p) 4 years (patient 2): Widening of the wrist joint; (r) 4 years (patient 2): Relatively enlarge intertarsal spaces; (s and l) 10 years (patient 6), (u) 13 years (patient 8): Enlarged interphangeal epiphyses, short distal phalanx.

Table 2 **List of homozygous pathogenic variants identified on the *COL11A2***

Family	Variant	Exon	Coding impact	Transcript	ACMG classification	References
I	c.3670C>T(p.Arg1224Ter)	52	nonsense	NM_080680.3	Likely pathogenic	10,11,12
II	c.3319del(p.Glu1107AsnfsTer131)	47	frameshift	NM_080681.3	Likely pathogenic	NR
III	c.2763del (p.Gly922ValfsTer62)	36	frameshift	NM_080680.3	Likely pathogenic	NR
IV	c.532del (p.Ser178ValfsTer11)	4	frameshift	NM_080681.3	Likely pathogenic	NR
V	c.1567C>T (p.Gln523Ter)	19	frameshift	NM_080681.3	Pathogenic	NR

NR, not reported.

Discussion

The age of manifestation of OSMEDB is variable ranging from birth to middle childhood. Although short extremities can also be identified in the perinatal period, there is NS number of studies in this field (Boyd *et al*., 2011). A considerable finding suggestive of skeletal dysplasias in antenatal ultrasonography is the short femur (Krakow *et al*., 2008). Short femura or short extremities were detected in all patients (5/5) in this cohort antenatally. OSMEDB patients may be recognized by short extremities and aplastic/ hypoplastic nasal bone in the prenatal period. On the other hand, it may be challenging to diagnose patients with antenatal clinical findings because there may be other skeletal dysplasias with similar findings in the differential diagnosis. We compared the height measurements and the slowdown in growth rates according to the age of three patients from the same family (family III, 2 siblings and 1 cousin). The 13-month-old patient's height was –1.22 SD, the 3-year-old's height was –0.85 SD, and the 7.5-year-old patient's height was –4.24 SD. However, the known birth height/weight of these three patients was not below the 3rd percentile. Although it is difficult to make a comment since there is no regular follow-up data on the patients, it could be speculated that short stature may become evident with mid-childhood, and show intrafamilial heterogeneity.

Among the similar facial features of all patients in this cohort, severe depression of the nasal bridge, which could be identified as a depressed nasal dorsum with shortened vertical nasal length, and loss of nasal tip support and projection is the most demonstrative finding. Major differential diagnoses with similar facial features accompanying short extremities are Stickler dysplasia and Kniest dysplasia. Rather than Stickler syndrome radiographic features favoring a diagnosis of OSMED are; more severe shortening of long bones, more severe vertebral anomalies, and distinct large epiphyses in childhood. Moreover, myopia

and vitreoretinal degeneration are features of Stickler dysplasia but not of OSMED. Otherwise, Kniest dysplasia manifests with a similar early phenotype. However, platyspondyly, shortness of the tubular bones, and metaphyseal widening are more severe in Kniest dysplasia than in OSMED. Severe myopia and other eye changes are not found in the latter.

The c.3991C>T, which has been a previously reported homozygous nonsense variant, was identified in P1 (Melkoniemi *et al*., 2000; Harel *et al*., 2005). Besides, three novel homozygous frameshift variants (c.3640del, c.2763del, and c.532del), and one novel homozygous nonsense variant (c.1567C>T) were described in this cohort. Loss of function is a known mechanism of disease and, these three null variants are extremely low allele frequency in gnomAD population databases. In two siblings with the c.3991C>T aged 3 and 7 years, the height was between −1.5 and 2 SD, had short limbs with enlarged joints, typical facial features, cleft palate, sensorineural hearing loss, and pectus excavatum. However, in 3-year-old P1 with the same variant, the height was at −1.1 SD and she did not have a cleft palate or pectus deformities.

Hearing loss is a known finding in OSMED. Although hearing loss in OSMED can often be detected congenitally, it can also occur later (Tokgoz-Yilmaz *et al*., 2011). The Joint Committee on Infant Hearing determined 10 risk indicators for audiological monitoring in infants until 2 years of age with normal hearing on newborn screening one of them is the presence of syndromic findings (Joint Committee on Infant Hearing, 2007). Although the diagnosis of hearing loss was verified in 7 of 8 patients, only one patient (P7) failed in neonatal hearing screening. Therewithal, hearing loss was realized in almost all of the patients after the 12th month.

As a consequence, OSMEDB is an extremely rare skeletal dysplasia with accompanying hearing loss. After reviewing the other cases in the literature, it was not concluded that there is a significant correlation between genotype and phenotype. There were severe speech delay and learning disabilities in two patients in this cohort and the hearing loss was realized after the age of 12 months. As a result, if hearing loss was identified as early as possible, the child could receive successful intervention.

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Informed consent has been obtained from patients that grant permission for the publication of images as part of this work.

Conflicts of interest

There are no conflicts of interest.

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