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Case Report

Foetal phenotype of Maat-Kievit-Brunner type Ohdo syndrome

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Abstract

MED12 is a member of large Mediator complex; has a very crucial and central role in RNA polymerase II transcription; regulating cell signals involved in growth, development and differentiation.

Different MED12 mutations may have different clinical presentation representing an allelic disorder.

Maat-Kievit-Brunner (MKB) type Ohdo syndrome; has a typical facial features comprising of blepharophimosis, ptosis, long flat philtrum with thin vermilion, micrognathia with microstomia, scrotal hypoplasia with cryptorchidism, joint hypermobility with clinodactyly with overriding toes,

A primigravida on antenatal ultrasound was detected to have growth restriction, corpus callosal dysgenesis, syndactyly and suspected ambiguous genitalia. Invasive testing and exome sequencing revealed *hg19chrX:MED12:c.2315A>G: (p.Lys772Arg);MED12(NM_005120.3):c.2315A>G: (p.Lys772Arg)* leading to provisional diagnosis of X linked Ohdo syndrome with an overlap with FG. Missense mutation was classified to be PM2; PP3 (ACMG)

Clinical presentation, phenotype and mutational analysis led to provisional diagnosis of X linked Ohdo syndrome. Maat-Kievit-Brunner type of Ohdo syndrome is a rare condition and this is probably the first case describing foetal phenotype of MKB type of Ohdo syndrome.

Key words: med12; allelic; mkb, ohdo syndrome; micrognathia; cryptorchidism; blepharophimosis; philtrum; vermilion, foetal; maat-kievit-brunner (mkb) type ohdo syndrome; blepharophimosis-mental retardation syndrome; x linked ohdo syndrome

Introduction

In 1974, Opitz and Kaveggia described a X-linked recessive intellectual disability syndrome characterized by relative macrocephaly, hypertelorism, downslant palpebral fissures, prominent forehead with frontal hair upsweep with broad thumbs and halluces [1].

In 1984, Lujan et al reported four male patients with marfanoid habitus, long narrow face, small mandible with high-arched palate, hypernasal voice with intellectual disability [2].

In 1993, Maat-Kievit et al delineated a X-linked Ohdo syndrome; characterized by failure to thrive with facial features comprising blepharophimosis, ptosis, wide depressed nasal bridge, long philtrum, thin vermilion, micrognathia with microstomia, scrotum hypoplasia with cryptorchidism, joint hypermobility, overriding toes with clinodactyly, cafe-au-lait spots, developmental delay with hearing disability [3].

In 2007, Risheg et al documented a recurrent *MED12* mutation (p.Arg961Trp) which was earlier diagnosed as FG (Opitz–Kaveggia)

syndrome [5]. Reported a different mutation (p.Gly958Glu) with similar clinical phenotype [4]. Demonstrated (p.Asn1007Ser) *MED12* mutation in a family originally diagnosed as Lujan–Fryns syndrome [6].

Vulto-van Silfhout [11] reported (p.Arg1148His, p.Ser1165Pro and p.His1729Asn) mutations in a family originally documented as MKB. [7] Isidor et al. identified (p.Arg1148His) mutation in two male siblings with phenotype similar to those of MKB [8].

It is now established that *MED12* mutations have different clinical presentation representing an allelic disorder. (Table 1) [9].

FG syndrome type 1 (FGS1)	Lujan syndrome (LS)	X-linked Ohdo syndrome
Craniofacial		
Small, simple ears, dolichocephaly, frontal hair upsweep, tall forehead, downslanted palpebral fissures, hypertelorism, high arched palate, micrognathia, narrow auditory canals, fullness of the upper eyelids, craniosynostosis	Tall narrow face, prominent nasal bridge, malar flattening, short philtrum, high narrow palate, dental crowding, and micrognathia. Hypotelorism, dolichocephaly, prominent forehead, downslanted palpebral fissures, ptosis, narrow nose, open mouth, double row of teeth, abnormal ears	Blepharophimosis, ptosis, epicanthal folds, low nasal bridge, broad nasal tip, small mouth, dental anomalies, maxillary hypoplasia, micrognathia, triangular face, high forehead, frontal hair upsweep, hypertelorism, high narrow palate, small posteriorly rotated ears, narrow auditory canals
Growth		
Absolute or relative macrocephaly, normal height to short stature	Large head circumference (>75th centile); typically tall, thin built with height (> 75th centile). Marfanoid habitus.	Normal growth to short stature to growth failure
Central nervous system		
Hypotonia; partial or complete agenesis of the corpus callosum	Hypotonia, abnormalities of corpus callosum and seizures	Microcephaly, Hypotonia, Corpus callosum dysgenesis (reported in one case) (8)
Ophthalmologic		
Strabismus, large corneas, optic atrophy, nystagmus, cataract, coloboma, phthisis bulbi, retinal detachment, decreased visual acuity	Strabismus	Strabismus, microphthalmia, and hypermetropia
Genitourinary		
Cryptorchidism and inguinal hernia	Small testes, large testes, and varicoceles	Cryptorchidism, small penis, and shawl scrotum
Present Case		
Established feature	**Identified Antenatally (Fig 1)**	**Identified Postnatally (Fig 2)**
Cryptorchidism, Scrotal hypoplasia	Ambiguous genitalia	Penoscrotal hypospadias
Clinodactyly, Overriding 3rd toes	Syndactyly 2&3rd toe, single feet	Confirmed
Low weight	Early onset growth retardation	
Blepharophimosis, Ptosis, Wide nasal bridge, Depressed nasal bridge, Large nose, Bulbous nose, Long philtrum, Flat philtrum, Thin vermilion		Blepharophimosis, low set ears, thin vermilion, long philtrum
Microstomia, Micrognathia		Micrognathia
Coarse facial features, Deafness, Feeding problems, Joint hyperextensibility, Cafe-au-lait spots		
Developmental delay, Mental retardation	Corpus callosum dysgenesis	*Isidor B etal. (2014) have reported corpus callosal dysgenesis in one case*
Antenatal and postnatal features of the foetus depicting an overlap between FG and Ohdo syndrome; corpus callosal abnormalities are not a classical feature of Ohdo syndrome however have been reported.		

Table 1 –*Characteristics Features of allelic disorders; FGS1, LS, Ohdo syndrome and Foetal features which were identified Antenatally and Postnatally*

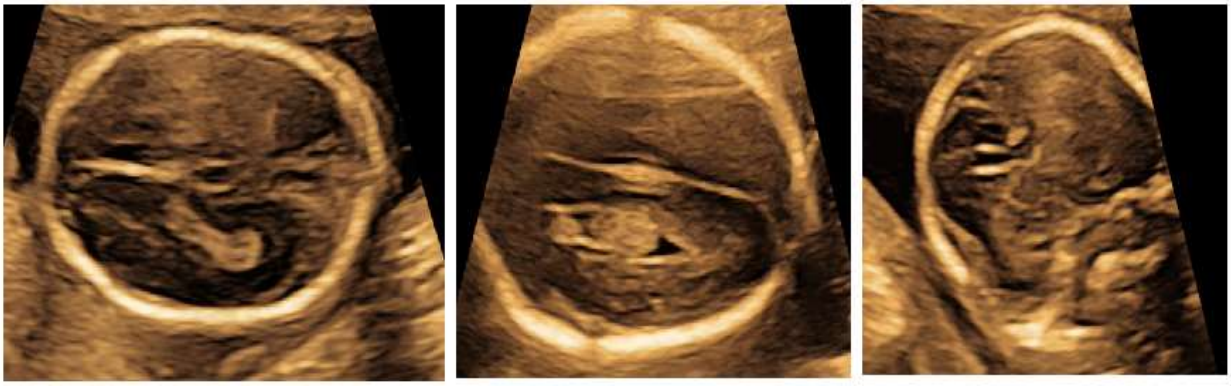
Maat-Kievit-Brunner (MKB) type Ohdo syndrome has a X-linked recessive inheritance pattern with typical facial features like thick alae nasi, blepharophimosis, ptosis, wide depressed nasal bridge, large bulbous nose, long flat philtrum with thin vermilion, micrognathia with microstomia, feeding difficulties, scrotal hypoplasia with cryptorchidism, joint hypermobility with clinodactyly with overriding toes, cafe-au-lait spots, hearing disability. Facial features become more pronounced with age with characteristic triangular facies [1]. It may have mild to severe developmental delay with delayed motor milestones with behavioural problems with mental retardation.

Maat-Kievit-Brunner type of Ohdo syndrome is a rare condition and this is probably the first case describing foetal phenotype of MKB type of Ohdo syndrome. It is caused *MED12* gene (mediator complex subunit 12) mutations; which is a subunit of the mediator complex, a group of about 25 proteins which regulates gene activity. It physically links transcription factors to turn on or off the genes. *MED12* protein is involved in development of the neurons, in several chemical signalling pathways to regulate cell growth, migration and differentiation.

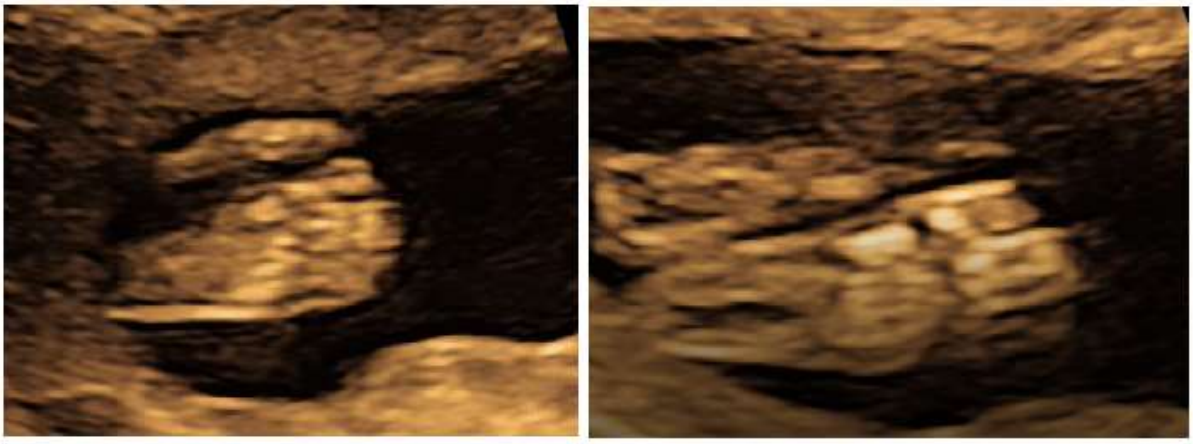
Case Report

A booked primigravida at 19 weeks of pregnancy with no high risk factor was evaluated in the department of Foetal Medicine at Artemis Hospital for foetal anomaly scan. It is a non-consanguineous marriage and no other male member of the extended family has been affected with intellectual disability or dysmorphism.

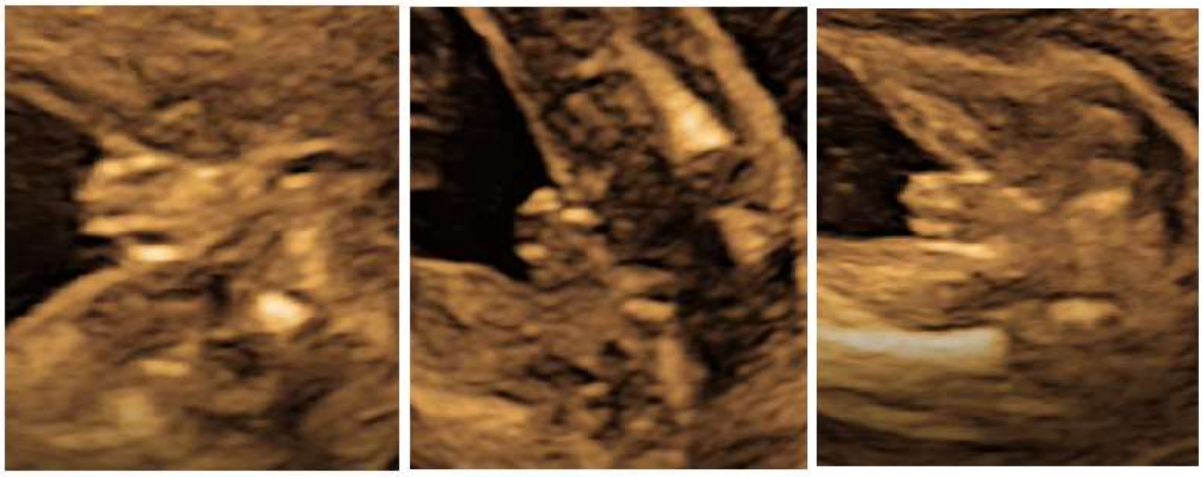
On antenatal ultrasound, high riding / upward displacement of 3rd ventricle was noticed with divergent frontal horns suggestive of corpus callosal dysgenesis (Figure 1-a). Further evaluation showed syndactly of 2 and 3rd toe of the right foot; however 2 and 3rd toes of the left foot were seen separate (Figure 1-b). Foetus was also identified to have hypospadias with suspected sex reversal or ambiguous genitalia (Fig 1-c). There was also an element of growth restriction by 1 week at 19 weeks of gestation (Figure 1-d).



(a)



Picture demonstrating syndactyly of 2&3 toes (b)



Ultrasound pictures depicting ambiguous genitalia / Sex reversal (c)

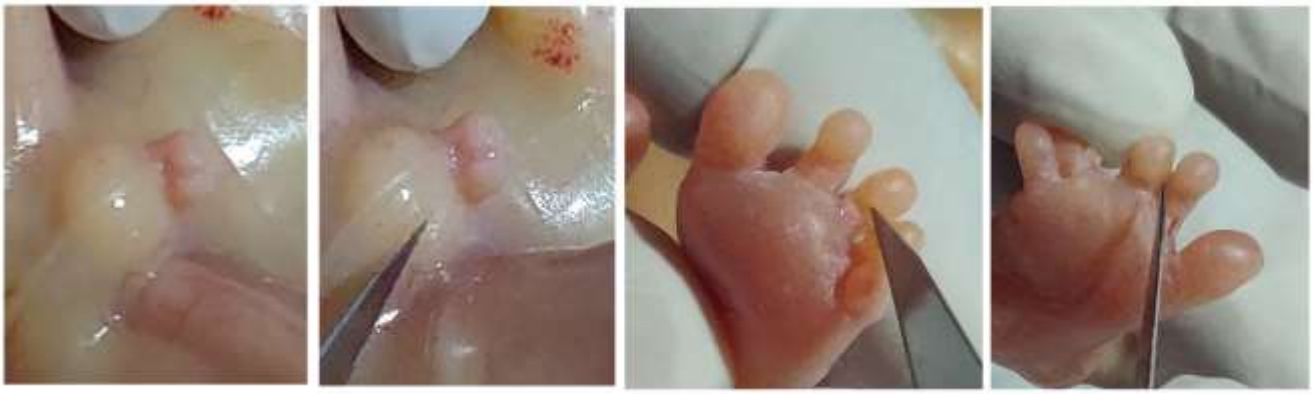
Antenatal ultrasound depicting growth restriction (d)

Figure 1 - *Antenatal examination of the foetus*

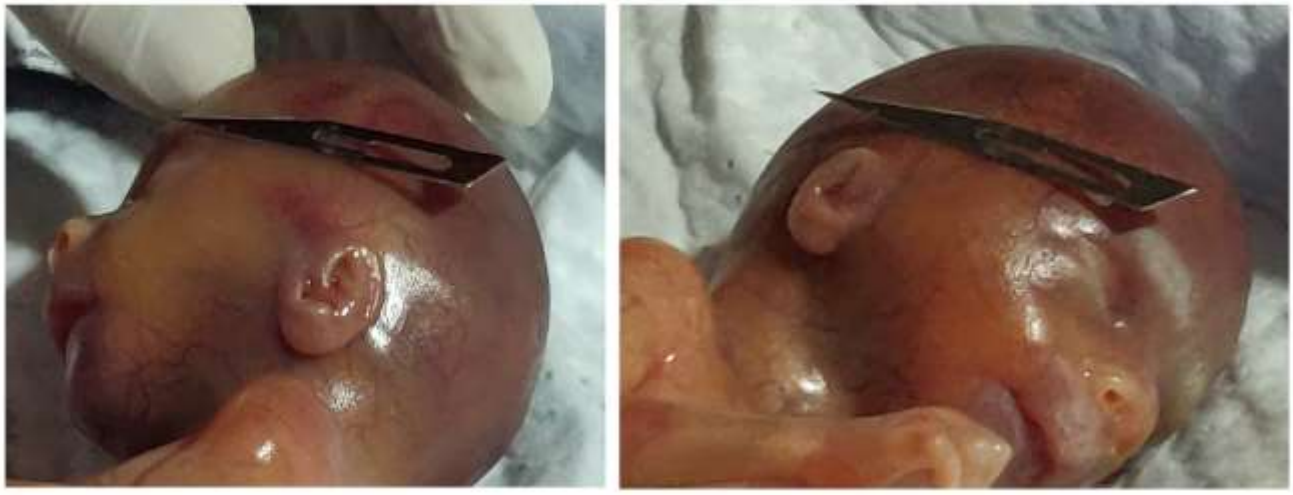
Axial scan of foetal brain showing high riding 3rd ventricle; upward displacement of the third ventricle; increased separation of the hemispheres, Coronal scan of a normal foetal brain demonstrating absence of the corpus callosum (genu), an increased distance between the frontal horns and their abnormal aspect suggestive of corpus callosal dysgenesis (a)

In the advent of foetal growth restriction, corpus callosal dysgenesis, syndactyly and suspected ambiguous genitalia; the consult and (parents) was counselled for invasive foetal testing; amniocentesis was done and on exclusion of maternal cell contamination; foetal DNA was processed for exome sequencing. Ambiguous genitalia in the clinical picture prompted and pointed towards foetal cholesterol pathway defect thus an exome sequencing was ordered. With all this information, possibilities couple decided for an irreversible decision regarding the pregnancy.

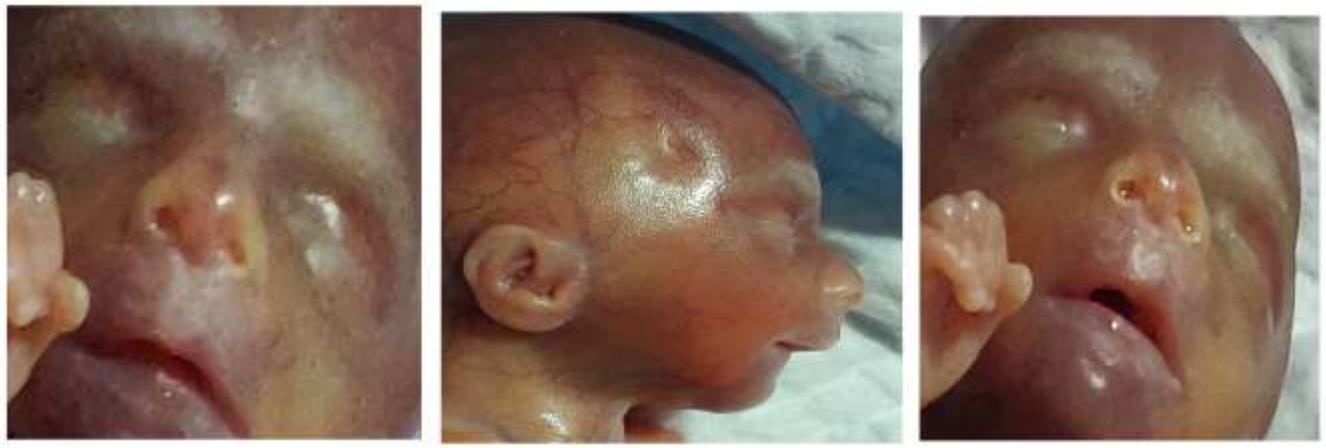
Postnatal examination of the foetus showed penoscrotal hypospadias, syndactyly in 2&3rd toe in the right feet and normally separated 2 and 3rd toe in the left toe (Figure 2-a) corroborating the main antenatal findings. It also revealed bilateral low set ears, micrognathia (Figure 2-b), thin vermilion, long philtrum and blepharophimosis (bilateral and both eye lids could not be separated completely with considerable effort) (Figure 2-c) corroborating the diagnosis of X linked Ohdo syndrome. The consult and (parents) gently refused for further postnatal (post mortem) examination of the foetus.



(a)



(b)



(c)

Figure 2 - *Postnatal examination of the foetus showing penoscrotal hypospadias, syndactyly in 2&3rd toe in right feet versus normal 2&3rd toe in left toe* **(a),** *bilateral low set ears, micrognathia* **(b),** *blepharophimosis, thin vermilion and long philtrum* **(c).**

Exome sequencing revealed hemizygous missense variation single-nucleotide variant (SNV) in exon 16 of the *MED12* gene (Xq13.1); with amino acid substitution of Arginine for Lysine at codon 772, c.2315A>G (p.Lys772Arg); *hg19chrX:MED12:c.2315A>G:(p.Lys772Arg); MED12(NM_005120.3):c.2315A>G:(p.Lys772Arg)* leading to provisional diagnosis of possible *MED12* related disorder; X linked Ohdo syndrome or FG syndrome.

The same mutation was confirmed by sanger sequencing and identified in the asymptomatic mother. In silico prediction of the variant has been identified to be damaging by LRT and Mutaion Taster.

In accordance to the American College of Medical Genetics and Genomics (ACMG) criteria for classifying pathogenic variants; the variation was classified as variant of uncertain significance and the missense mutation was classified to be PM2 (absent from controls or at extremely low frequency if recessive) and PP3 *(*multiple lines of computational evidence support a deleterious effect on the gene or gene product). (19)

Table no 1 elaborates characteristic features of the Ohdo syndrome; some of which detected antenatally were confirmed and remaining were identified by postnatal examination. Maat-Kievit et al. (1993), Verloes et al. (2006) and Vulto-van Silfhout et al. (2013) (3, 7, 14) have reported missense mutations in MED 12 to be causative for Maat-Kievit-Brunner type Ohdo syndrome (Table 2). Table no 3 describes the genotype – phenotype corelation of MED 12 mutations.

No of subjects	Type of mutation	Mutation	PolyPhen-2 (9)	SIFT (10)	Authors
2 males; postnatal	hemizygous c.3443G-A missense	arg1148-to-his (R1148H)	probably damaging	deleterious	Maat-Kievit et al. (1993) (3)
2 males; postnatal	hemizygous c.3493T-C missence	ser1165-to-pro (S1165P)	probably damaging	deleterious	Verloes et al. (2006) (14)
9 simplex male; postnatal	hemizygous de novo c.5185C-A transversion	his1729-to-asn (H1729N)	probably damaging	deleterious	Vulto-van Silfhout et al. (2013) (7)
Present case 1 male; Antenatal	hemizygous c.2315A-G missense	Exon 16; (p.Lys772Arg)	probably damaging	deleterious	Confirmed by Sanger; identified the same mutation in mother

Table 2 – *MED 12 mutations reported by other Authors and the present case*

DNA Nucleotide Change	Predicted Protein Change	Characteristic features	Reference
c.2444G>A	p.Arg815Gln		(11)
c.2873G>A	p.Gly958Glu	Opitz-Kaveggia syndrome X-linked inheritance Tall forehead, frontal hair upsweep, long narrow face, open mouth, small simple ears, absolute or relative macrocephaly, congenital anomalies of corpus callosum, heart, anus, skeleton, behavioural problems, hypotonia, constipation, feeding problems	(5)
c.2881C>T	p.Arg961Trp	Opitz-Kaveggia syndrome (FG syndrome) X-linked disorder; multiple congenital anomaly-cognitive impairment disorder	(4,12)

		Mental retardation, relative macrocephaly, hypotonia and constipation. Family history of deceased male infants, multiple foetal losses Tall forehead, frontal hair upsweep, long narrow face, open mouth, small simple ears, absolute or relative macrocephaly, congenital anomalies of corpus callosum, heart, anus, skeleton, behavioural problems, hypotonia, constipation, feeding problems	
c.3020A>G	p.Asn1007Ser	Lujan (Lujan-Fryns) syndrome Tall stature with asthenic habitus, macrocephaly, tall narrow face, maxillary hypoplasia, high narrow palate, dental crowding, receding chin, long hands with hyperextensible digits, hypernasal speech, hypotonia, mild-to-moderate mental retardation, behavioural problems, dysgenesis of the corpus callosum. Overlapping features with FG syndrome - dysgenesis of the corpus callosum, relative macrocephaly, tall forehead, hypotonia, mental retardation , behavioural disturbances.	(6)
c.3067A>G	p.Ile1023Val	X-linked recessive intellectual disability syndrome; dysmorphic features long, narrow face, blepharophimosis	(13)
c.3443G>A	p.Arg1148His	Ohdo syndrome Intellectual disability; typical facial features, blepharophimosis. Short humeri, dysmorphic features, blepharophimosis, Hirschsprung disease, intellectual disability, hypotonia, behaviour issues, blepharophimosis, ptosis, facial coarsening, and thick alae nasi	(3,7,8,14)
c.3493T>C	p.Ser1165Pro		
c.5185C>A	p.His1729Asn		
c.4147G>A	p.Ala1383Thr	Ohdo syndrome Feeding difficulties, microcephaly, speech delay, hypertonia, eosinophilic esophagitis, penile chordee, facial dysmorphisms Represent a new phenotype, reflecting a spectrum of characteristics	(15)
c.5898dupC	p.Ser1967GlnfsTer84	FG, Lujan, Ohdo syndrome, the Maat-Kievit-Brunner type, are described as distinct syndromes with overlapping phenotype and different missense mutations of the MED12 gene Long narrow face, high forehead, flat malar area, high nasal bridge, short philtrum, very limited language, cognitive impairment	(16)
c.5922G>T	p.Gln1974His	X-linked intellectual deficiency (XLID) MED12 gene causes syndromic and nonsyndromic forms of XLID	(17)
c.3883C > T	p.(Arg1295Cys	Mild to severe ID, speech delay, behavioural problems, dysmorphic facial features, hearing loss	(18)
Present Case		**Features identified antenatally**	**Features identified postnatally**
c.2315A-G	p.Lys772Arg	Ambiguous genitalia, Syndactyly 2&3rd toe, single feet, Early onset growth retardation, Corpus callosum dysgenesis [Isidor B etal. (2014)]	Penoscrotal hypospadias, Blepharophimosis, low set ears, thin vermilion, long philtrum, Micrognathia

Table 3 – *Genotype – Phenotype corelation of the MED 12 mutations*

Clinical presentation, phenotype and mutational analysis led to provisional diagnosis of possible *MED12* related disorder; X linked Ohdo syndrome or FG syndrome.

Discussion

MED12 being a member of large Mediator complex; has a very crucial and central role in RNA polymerase II transcription. It regulates the cell signals involved in growth, development and differentiation.

MKB is a rare condition; X-linked recessive inheritance; very typical pattern of facial features which are difficult to be detected on antenatally. It is probably the first case of detection of foetal phenotype of MKB.

With ever increasing use of massive parallel sequencing with next-generation sequencers, it is likely that more *MED12* distinctive phenotype and mutations will be detected. This also helps in identifying the genetic aetiology in families with intellectual disability and dysmorphic features and to broaden genotype–phenotype correlations.

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