MedPeer Publishers
Empowering Evidence-Based Medicine Through Peer-Reviewed Excellence

Open Access Case Report

MedPeer Publisher
Abbreviated Key Title: MedPeer
ISSN : 3066-2737
homepage: https://www.medpeerpublishers.com

ORAL-FACIAL-DIGITAL SYNDROME TYPE IV ASSOCIATED WITH DANDY-WALKER MALFORMATION: A RARE PRESENTATION IN A CONSANGUINEOUS MOROCCAN FAMILY

DOI: 10.70780/medpeer.000QGYI

AUTHOR AND AFFILIATION

Kenza Dafir[1,4,*], Fatima Zahrae Bouzid[2,4], Fatiha Bennaoui[3,4], Nisrine Aboussair[2,4]
[1] Department of Genetics, Avicenna Military Hospital, Marrakech, Morocco
[2] Department of Genetics, Clinical Research Centre, Mohammed VI University Hospital, Marrakech, Morocco
[3] Department of Neonatal Intensive Care, Mother and Child Hospital, Mohammed VI University Hospital, Marrakech, Morocco
[4] Faculty of Medicine and Pharmacy of Marrakech, Cadi Ayyad University, Marrakech, Morocco
[*] Corresponding author: Kenza Dafir.

ABSTRACT

Introduction: Oral-facial-digital syndromes (OFDS) are a heterogeneous group of ciliopathies defined by malformations of the oral cavity, face and digits. OFD type IV (OFD IV, Mohr-Majewski or Baraitser-Burn syndrome) is a very rare autosomal recessive form, distinguished by tibial dysplasia. Its main known cause is biallelic variants in *TCTN3*.

Case presentation: A consanguineous couple (first cousins) was referred for genetic counselling after two neonatal deaths in a context of multiple malformations. In the third pregnancy, prenatal ultrasound at 32–33 weeks showed cerebral malformations. The male newborn had a cleft palate, a lobulated tongue, lingual and gingival frenula, neonatal teeth, bilateral postaxial hexadactyly of the hands and tibial hypoplasia. Imaging showed a Dandy-Walker malformation with agenesis of the cerebellar vermis and of the corpus callosum and intracerebral cysts, and an atrial septal defect. Laryngeal fibroscopy showed laryngeal hypoplasia. Renal ultrasound was normal and the parents' karyotypes were normal. The child died at 3 months and 9 days from respiratory distress related to the laryngeal hypoplasia. The diagnosis of OFD IV was made on clinical grounds; DNA was stored, but molecular testing could not be performed for financial reasons.

Conclusion: This case adds a family with OFD IV to the small number reported, with recurrence in three siblings and a severe cerebral malformation not previously described in the cases we reviewed. In families with a suggestive phenotype, careful clinical and radiological evaluation, including the tibiae and the posterior fossa, guides the diagnosis among overlapping ciliopathies. Genetic counselling must inform the couple of a 25% recurrence risk, and molecular confirmation would allow carrier testing and early prenatal diagnosis.

KEYWORDS
oral-facial-digital syndrome type IV, Mohr-Majewski syndrome, *TCTN3*, ciliopathy, tibial hypoplasia, Dandy-Walker malformation, consanguinity, genetic counselling

MAIN ARTICLE

INTRODUCTION

Oral-facial-digital syndromes (OFDS) result from a disturbance of development that almost always affects the mouth, the face and the digits; involvement of other organs defines the different types [1]. Thirteen types were initially distinguished on clinical grounds [1]. Since then, at least 16 causal genes have been identified, all involved in the structure or function of the primary cilium, and OFDS are now considered a distinct subgroup of ciliopathies [2,3]. Because the clinical types overlap widely, it has been proposed to restrict the clinical classification to the three best-delineated subtypes and to classify other patients according to their genotype [3].

OFD type IV (OMIM 258860) was described in 1984 by Burn et al. in two sisters born to first-cousin parents, who had unusual facies, tongue hamartomas, pre- and postaxial polydactyly, severe talipes and mesomelic limb shortening with tibial dysplasia [4]. The condition is also known as Baraitser-Burn syndrome, Mohr-Majewski syndrome, or OFD syndrome with tibial defects [5]. Its autosomal recessive inheritance and severe tibial dysplasia distinguish it from OFD type I [5]. In 2012, Thomas et al. identified biallelic *TCTN3* variants in patients with OFD IV; TCTN3 is a protein of the ciliary transition zone required for Sonic Hedgehog signalling [6]. However, the condition appears genetically heterogeneous [5].

OFD IV must be distinguished from OFD type VI, a subtype of Joubert syndrome defined by the molar tooth sign on brain imaging [7], and from Meckel-Gruber syndrome, another lethal ciliopathy. OFD IV is very rare: Nevin and Thomas reported the fifth case in 1989 [8], and Digilio et al. the tenth in 1995 [9]; since then, only isolated patients and families have been published. We report a consanguineous family from southern Morocco with three affected children and discuss the diagnosis in light of the literature. This report is of interest for four reasons: it adds a new family to the small number described; it shows recurrence in three siblings of both sexes born to first-cousin parents, which supports autosomal recessive inheritance; the proband had a Dandy-Walker malformation with agenesis of the vermis and corpus callosum, an association we did not find in the published cases we reviewed; and it documents the condition in a family from southern Morocco, a population in which consanguinity is frequent and molecular testing is often not accessible.

CASE PRESENTATION

Family history

A couple from southern Morocco was referred to our genetics clinic for genetic counselling. The mother was 21 years old and the father 50 years old. They are first cousins: their mothers are sisters (Figure 1). Their first two children, a boy and a girl, died in the neonatal period with multiple malformations; their medical records were not available, and their exact phenotype could not be documented. The father has two healthy daughters from a previous union. There was no other similar case in the family. The karyotypes of both parents were normal.

Pregnancy and birth

The third pregnancy was followed in our centre. The morphological ultrasound at 32–33 weeks of gestation showed cerebral malformations. The couple received counselling, and delivery was planned in a centre with neonatal care. The baby was born vaginally at 39 weeks of gestation, in January 2020. Birth weight was 2900 g, length 48 cm and head circumference 34 cm, all within normal ranges.

Clinical examination

The male newborn had facial dysmorphism with hypertelorism, a broad nasal root, a bulbous nose and low-set ears. The upper lip was intact. Oral examination showed a cleft palate, a lobulated tongue with hamartomatous nodules, multiple lingual and gingival frenula, and neonatal teeth (Figure 2A and 2B). The limbs showed bilateral postaxial hexadactyly of the hands (Figure 2C and 2D), brachydactyly, and shortening and deformity of the legs. Radiographs of the lower limbs confirmed bilateral tibial hypoplasia.

Investigations

Brain computed tomography (CT) showed a Dandy-Walker malformation with agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle and an enlarged posterior fossa, together with agenesis of the corpus callosum and intracerebral cysts (Figure 3). No molar tooth sign was described. Echocardiography showed an atrial septal defect. Abdominal ultrasound was normal, with normal kidneys and liver. Fundus examination was normal. Laryngeal fibroscopy showed laryngeal hypoplasia.

Outcome

The child died at 3 months and 9 days of life from respiratory distress related to the laryngeal hypoplasia. A DNA sample was extracted and stored for molecular analysis. Molecular testing

(targeted sequencing of *TCTN3* or a ciliopathy gene panel/exome) could not be performed, because the family could not cover its cost.

Diagnosis

The association of oral anomalies (cleft palate, lobulated tongue, multiple frenula and neonatal teeth), postaxial polydactyly and tibial hypoplasia, with recurrence in siblings of both sexes born to consanguineous parents, led to the clinical diagnosis of OFD type IV, with severe cerebral involvement.

DISCUSSION

A clinical diagnosis of OFD type IV

The diagnosis of OFD type IV rests on the combination of oral, facial and digital anomalies with tibial dysplasia, in the context of autosomal recessive inheritance [4,5]. Our patient had all of these elements. The lobulated tongue, the oral frenula and the cleft palate are oral features common to the OFD group [1,10]. Postaxial polydactyly of the hands is frequent in OFD IV, often with preaxial polydactyly or polydactyly of the feet [4,8,10]. Tibial dysplasia is considered the pivotal feature of OFD IV [11]. Finally, the recurrence in a boy and a girl born to first cousins supports autosomal recessive inheritance. Many reported OFD IV families are consanguineous [10].

Comparison with reported cases

OFD IV is very rare, and most publications describe one patient or one sibship. Table 2 compares our patient with the main reports.

Our patient shares the core features of all reported cases: oral anomalies, polydactyly and tibial involvement [4,6,8–10,12]. As in the family reported by Ozdemir-Karatas et al., in which three children and two fetuses with the same phenotype had died, several children of the sibship were affected and died early, which illustrates the severity of the condition [10]. The main particularity of our case is the severity of the brain malformation. Cerebral anomalies are not part of the original description [4], but they have been reported repeatedly: Digilio et al. described cerebral anomalies associated with joint dislocations [9], neuropathological examination in another reported case revealed agenesis of the corpus callosum and hypoplasia of the vermis [5], and the index case of Thomas et al. had an occipital encephalocele and other brain anomalies [6]. The Dandy-Walker malformation with agenesis of the vermis and of the corpus callosum in our patient therefore fits within the spectrum of OFD IV, at its severe end. The atrial septal defect is also consistent with the congenital heart defects reported in severe

forms [12]. The laryngeal hypoplasia, which caused the death of our patient, was also present in the severely affected infant reported by Meinecke and Hayek, who had a hypoplastic larynx and epiglottis [12]; absent or hypoplastic epiglottis is also listed among the oral features of OFD IV [10]. Conversely, our patient had normal kidneys and no anal anomaly, features reported in severe forms [9,12].

Toriello et al. described six children diagnosed with OFD IV, all with oral, facial, digital and tibial defects, and concluded that they probably had different conditions [5]. Severe forms overlap with Majewski-type short rib-polydactyly syndrome [12], and some fetal cases overlap with Meckel syndrome [6].

Differential diagnosis

The main conditions to consider are summarised in Table 3.

OFD type VI (Váradi-Papp syndrome). OFD VI is a subtype of Joubert syndrome and related disorders. Its diagnostic criteria are the molar tooth sign together with at least one of the following: tongue hamartoma(s), additional frenula or upper lip notch; mesoaxial polydactyly; hypothalamic hamartoma [7]. Tongue hamartomas, additional frenula, upper lip notch and mesoaxial polydactyly are considered specific to OFD VI, whereas cleft lip/palate and other types of polydactyly are not [7]. Our patient did have tongue nodules and multiple frenula; however, his polydactyly was postaxial, no molar tooth sign was seen on CT, and tibial hypoplasia is not a feature of OFD VI. However, CT is less sensitive than magnetic resonance imaging (MRI) for the molar tooth sign, and a mild form could not be excluded. Overlap between OFD IV and OFD VI has also been reported at the molecular level: a patient with biallelic *TMEM107* variants (OFD type XVI) had both tibial dysplasia and a molar tooth sign [11].

Joubert syndrome. Joubert syndrome is defined by the molar tooth sign and is associated with hypotonia, abnormal breathing and developmental delay [13]. The absence of the molar tooth sign argues against this diagnosis, although only MRI can exclude it.

Meckel-Gruber syndrome. This lethal ciliopathy classically associates occipital encephalocele, cystic kidneys and polydactyly [14]. Our patient had no encephalocele, and his kidneys and liver were normal on ultrasound.

Short rib-polydactyly syndrome type II (Majewski). This lethal recessive disorder is characterised by short ribs and polydactyly, and severe forms of OFD IV overlap with it

[10,12]. The survival of our patient to 3 months, without reported thoracic hypoplasia, makes it less likely.

OFD type I and OFD type II (Mohr syndrome). OFD I is X-linked dominant and generally lethal in males; it is associated with polycystic kidney disease [2,3]. Two affected boys in the sibship argue strongly against it. OFD II shares the oral anomalies and polydactyly, whereas tibial dysplasia is the pivotal feature of OFD IV [11].

Genetic basis and molecular confirmation

TCTN3 encodes tectonic-3, a component of the transition zone at the base of the primary cilium. Its disruption impairs Sonic Hedgehog signalling and causes a severe ciliopathy with features of both Meckel syndrome and OFD IV [6]. In the study of Thomas et al., truncating variants were found in fetuses with overlapping Meckel and OFD IV features, and a homozygous missense variant was found in a family with Joubert syndrome [6]. Other genes may be involved, given the genetic heterogeneity of OFD IV [3,5]. In this context, exome sequencing, or a large ciliopathy gene panel, is the most efficient approach, with *TCTN3* as the first candidate gene.

In our patient, the diagnosis remains clinical, because molecular testing could not be funded. This is a common situation in Morocco, where consanguinity is frequent: 15.25% of marriages nationally, and 59% among families affected by autosomal recessive disorders [15]. The DNA of the proband has been stored, so that testing can be carried out when funding becomes available.

Genetic counselling and prenatal diagnosis

OFD IV is autosomal recessive. Both parents are presumed heterozygous carriers, and the recurrence risk is 25% for each pregnancy. Identification of the familial variants would allow carrier testing of relatives and molecular prenatal diagnosis on chorionic villi, or preimplantation genetic testing.

Until then, prenatal diagnosis relies on ultrasound. Targeted examination of the next pregnancies should look for polydactyly, short tibiae, oral clefts, and posterior fossa and corpus callosum anomalies from the late first trimester. In our case, the cerebral malformations were detected only at 32–33 weeks, which underlines the importance of early, targeted ultrasound by an experienced operator in at-risk pregnancies.

Limitations

The main limitation of this report is the absence of molecular confirmation. In addition, brain MRI was not performed, so the molar tooth sign could not be formally excluded. The deceased siblings could not be examined and their records were not available, so their diagnosis rests on the family history.

CONCLUSION

We report a consanguineous Moroccan family in which three children were affected by OFD type IV, diagnosed on the combination of oral anomalies, postaxial polydactyly and tibial hypoplasia. The proband also had a Dandy-Walker malformation with agenesis of the vermis and of the corpus callosum, and died from laryngeal hypoplasia, which places this case at the severe end of the spectrum. This observation highlights the role of the genetics consultation in establishing the diagnosis, giving appropriate genetic counselling and planning early prenatal diagnosis. Molecular testing, ideally by exome sequencing, would confirm the diagnosis and allow carrier testing in this family.

LEARNING POINTS

- OFD IV should be considered in any newborn with oral anomalies (lobulated tongue, frenula, cleft palate), polydactyly and short or bowed legs; radiographs of the tibiae are essential.
- Brain imaging, ideally MRI, is needed to look for a molar tooth sign and to distinguish OFD IV from OFD VI and Joubert syndrome.
- Laryngeal hypoplasia can be part of OFD IV and can be life-threatening: early airway assessment is warranted in affected newborns.
- In consanguineous families, recurrence of a multiple malformation syndrome should prompt genetic counselling, DNA storage and early, targeted ultrasound in subsequent pregnancies.

FIGURES:

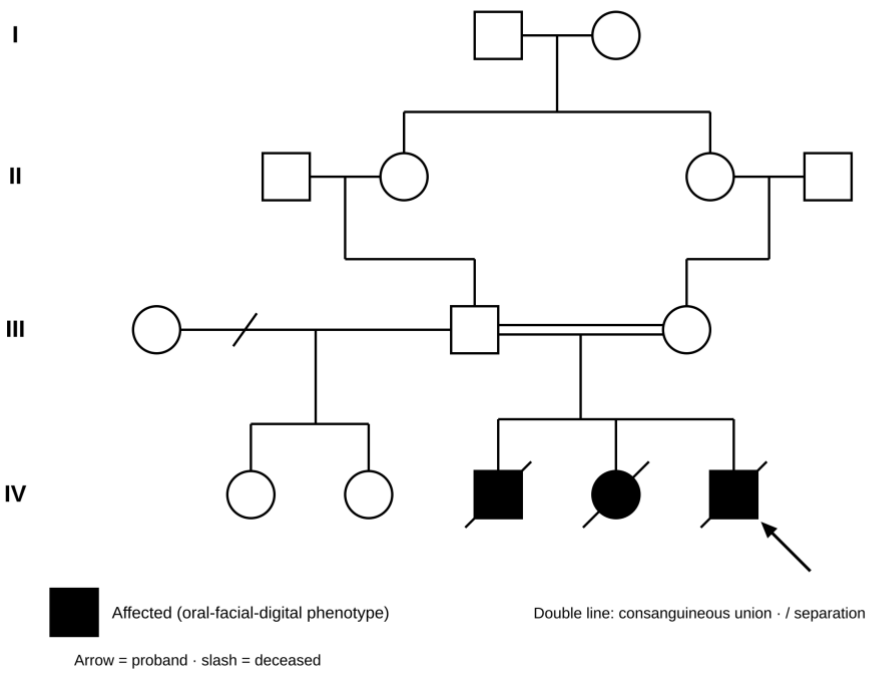


Figure 1: Pedigree of the family. The parents (III) are first cousins. Their three children were affected and died; the proband (arrow) died at 3 months. The father has two healthy daughters from a previous union.

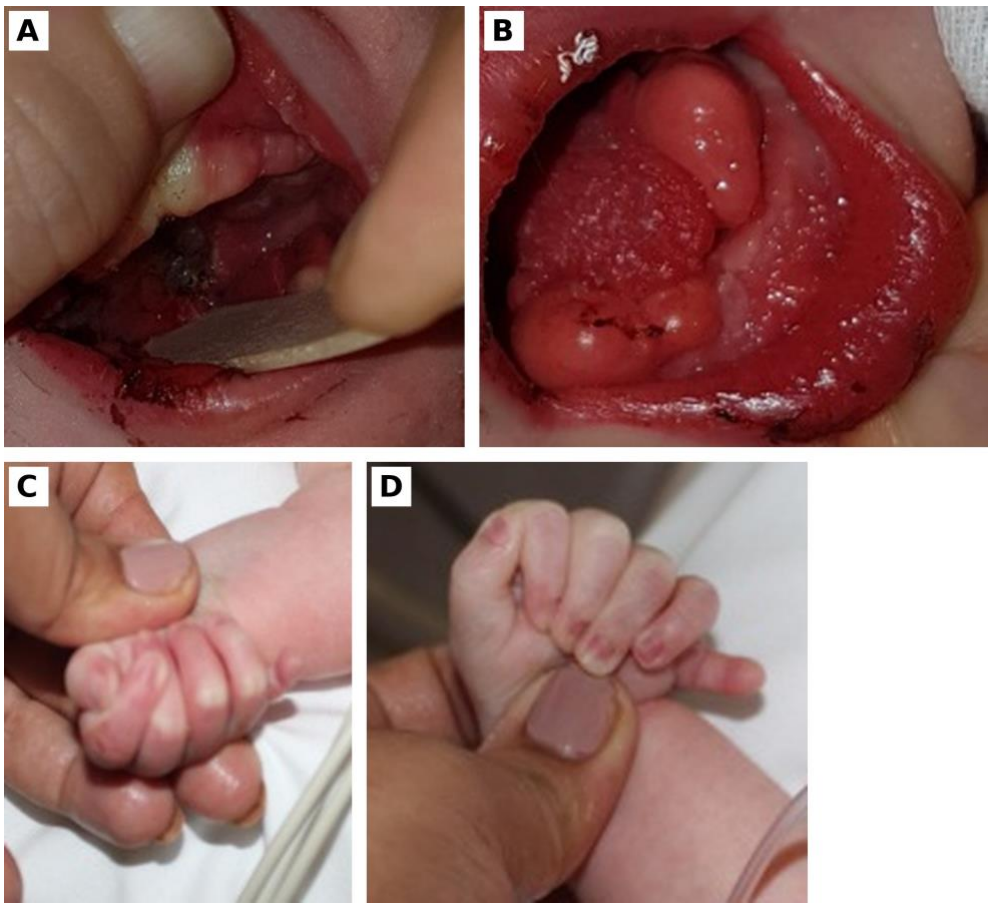


Figure 2: Clinical features of the proband. (A) Oral cavity showing the cleft palate, gingival frenula and neonatal teeth. (B) Lobulated tongue with hamartomatous nodules. (C, D) Hands with postaxial polydactyly.

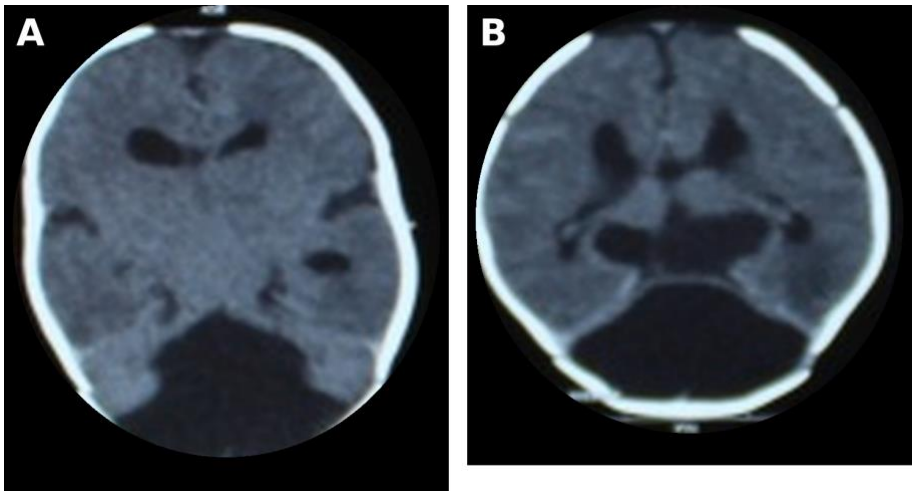


Figure 3: Brain computed tomography of the proband (axial sections). (A) Large cystic posterior fossa communicating with the fourth ventricle, with absent cerebellar vermis. (B) Enlarged posterior fossa and abnormal configuration of the lateral ventricles, consistent with agenesis of the corpus callosum.

TABLES :

Table 1 : Timeline of the case

Period	Events
Before the third pregnancy	Two children (a boy and a girl) died in the neonatal period with multiple malformations
Third pregnancy	Genetic counselling; morphological ultrasound at 32–33 weeks showing cerebral malformations; delivery planned in a centre with neonatal care
Birth (January 2020, 39 weeks)	Male newborn: oral anomalies, postaxial hexadactyly of the hands, leg shortening
Neonatal period	Lower-limb radiographs (tibial hypoplasia), brain CT (Dandy-Walker malformation), echocardiography (atrial septal defect), abdominal ultrasound and fundus (normal), laryngeal fibroscopy (laryngeal hypoplasia); clinical diagnosis of OFD IV; DNA stored
3 months and 9 days	Death from respiratory distress related to laryngeal hypoplasia

Table 2 : Comparison of our patient with published cases of OFD type IV

Feature	Our case	Burn 1984 [4]	Nevin 1989 [8]	Meinecke 1990 [12]	Digilio 1995 [9]	Thomas 2012[a] [6]	Ozdemir-Karatas 2014 [10]
Sex	M	2 F (sisters)	NR	M	F	M (fetus)	F
Parental consanguinity	Yes (first cousins)	Yes (first cousins)	NR	NR	NR	Yes	Yes (first cousins)
Affected siblings	2 (deceased)	2 sisters	NR	NR	NR	NR	3 deceased children and 2 fetuses
Lobulated tongue / hamartoma	+	+	+	+	+[b]	+	+
Cleft lip or pseudo-cleft	–	NR	+	+	NR	NR	+ (pseudo-cleft)
Cleft palate	+	NR	NR	+	NR	NR	+
Oral frenula	+	NR	NR	NR	NR	NR	+
Polydactyly	Postaxial, hands	Pre- and postaxial	Pre- and postaxial, hands and feet	Hands	+[b]	Four limbs	Pre- and postaxial, hands and feet
Tibial hypoplasia / dysplasia	+	+	+	+ (short, broad)	+[b]	+ (hypoplasia, bowing of long bones)	+ (short, broad)
Brain anomalies	DWM, vermis and CC agenesis, cysts	NR	NR	NR	+	Occipital encephalocele, others	– (normal MRI)
Heart defect	ASD	NR	NR	Severe CHD	NR	NR	–
Kidney anomalies	–	NR	NR	Renal agenesis	+	Cystic kidneys	–

Feature	Our case	Burn 1984 [4]	Nevin 1989 [8]	Meinecke 1990 [12]	Digilio 1995 [9]	Thomas 2012[a] [6]	Ozdemir-Karatas 2014 [10]
Other	Neonatal teeth, brachydactyly, laryngeal hypoplasia	Talipes	Talipes, deafness	Larynx hypoplasia, anal atresia	Anal atresia, joint dislocations	Ductal plate proliferation in the liver	Oligodontia, talipes, conductive hearing loss
Outcome	Died at 3 mo	NR	NR	NR	NR	TOP at 19 wk	Alive at 6 y

M, male; F, female; NR, not reported in the sources consulted; DWM, Dandy-Walker malformation; CC, corpus callosum; ASD, atrial septal defect; CHD, congenital heart defect; TOP, termination of pregnancy; wk, weeks; mo, months; y, years. [a] Index case in which *TCTN3* variants were identified. [b] Reported as typical features of the syndrome; details not available in the abstract.

Table 3 : Differential diagnosis: main features of the overlapping conditions compared with our patient

Feature	Our patient	OFD IV	OFD VI	Joubert syndrome	Meckel-Gruber syndrome	SRPS type II (Majewski)	OFD I
Inheritance	Presumed AR (affected siblings of both sexes, consanguinity)	AR [5]	Mostly AR [2]	AR or X-linked [13]	AR [14]	Recessive [10]	X-linked dominant, male-lethal [2]
Defining features	Oral anomalies, postaxial polydactyly, tibial hypoplasia	Tibial dysplasia (pivotal feature) [11]	Molar tooth sign + oral findings, mesoaxial polydactyly or hypothalamic hamartoma [7]	Molar tooth sign [13]	Occipital encephalocele, cystic kidneys, polydactyly [14]	Short ribs, polydactyly [10]	Oral, facial and digital anomalies; polycystic kidneys [2,3]
Molar tooth sign	Not seen on CT (MRI not done)	Not required	Required [7]	Required [13]	–	–	–
Kidneys	Normal	Cystic in severe fetal forms [6]	–	–	Cystic [14]	–	Polycystic [2]
Arguments against, in our patient	–	–	Postaxial (not mesoaxial) polydactyly, no molar tooth sign on CT, tibial hypoplasia	No molar tooth sign on CT	No encephalocele, normal kidneys	Survival to 3 months, no thoracic hypoplasia reported	Two affected boys in the sibship

AR, autosomal recessive; CT, computed tomography; MRI, magnetic resonance imaging; SRPS, short rib-polydactyly syndrome; –, not a defining feature.

DECLARATIONS

Consent: Clinical information and illustrative photographs were handled in accordance with patient confidentiality and ethical considerations. No identifiable images of the patient are presented in this article.

Conflicts of interest: the authors declare no conflict of interest.

Funding: none.

REFERENCES

1. Gurrieri F, Franco B, Toriello H, Neri G. Oral-facial-digital syndromes: review and diagnostic guidelines. Am J Med Genet A. 2007;143A(24):3314–3323. doi:10.1002/ajmg.a.32032
2. Franco B, Thauvin-Robinet C. Update on oral-facial-digital syndromes (OFDS). Cilia. 2016;5:12. doi:10.1186/s13630-016-0034-4
3. Bruel AL, Franco B, Duffourd Y, Thevenon J, Jego L, Lopez E, et al. Fifteen years of research on oral-facial-digital syndromes: from 1 to 16 causal genes. J Med Genet. 2017;54(6):371–380. doi:10.1136/jmedgenet-2016-104436
4. Burn J, Dezateux C, Hall CM, Baraitser M. Orofaciodigital syndrome with mesomelic limb shortening. J Med Genet. 1984;21(3):189–192. doi:10.1136/jmg.21.3.189
5. Online Mendelian Inheritance in Man (OMIM). Orofaciodigital syndrome IV; OFD4. MIM number 258860. Baltimore (MD): Johns Hopkins University. https://omim.org/entry/258860 (accessed 18 November 2026).
6. Thomas S, Legendre M, Saunier S, Bessières B, Alby C, Bonnière M, et al. TCTN3 mutations cause Mohr-Majewski syndrome. Am J Hum Genet. 2012;91(2):372–378. doi:10.1016/j.ajhg.2012.06.017
7. Poretti A, Vitiello G, Hennekam RCM, Arrigoni F, Bertini E, Borgatti R, et al. Delineation and diagnostic criteria of oral-facial-digital syndrome type VI. Orphanet J Rare Dis. 2012;7:4. doi:10.1186/1750-1172-7-4
8. Nevin NC, Thomas PS. Orofaciodigital syndrome type IV: report of a patient. Am J Med Genet. 1989;32(2):151–154. doi:10.1002/ajmg.1320320202
9. Digilio MC, Giannotti A, Pagnotta G, Mingarelli R, Dallapiccola B. Joint dislocation and cerebral anomalies are consistently associated with oral-facial-digital syndrome type IV. Clin Genet. 1995;48:156–159.
10. Ozdemir-Karatas M, Ozdemir-Ozenen D, Hart PS, Hart TC. Craniodentofacial manifestations in a rare syndrome: orofaciodigital type IV (Mohr-Majewski syndrome). Case Rep Dent. 2014;2014:605892. doi:10.1155/2014/605892
11. Chinen Y, Nakamura S, Yanagi K, Kaneshi T, Goya H, Yoshida T, et al. Additional findings of tibial dysplasia in a male with orofaciodigital syndrome type XVI. Hum Genome Var. 2022;9. doi:10.1038/s41439-022-00187-9
12. Meinecke P, Hayek H. Orofaciodigital syndrome type IV (Mohr-Majewski syndrome) with severe expression expanding the known spectrum of anomalies. J Med Genet. 1990;27(3):200–202. doi:10.1136/jmg.27.3.200
13. Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol. 2013;12(9):894–905. doi:10.1016/S1474-4422(13)70136-4

14. Hartill V, Szymanska K, Sharif SM, Wheway G, Johnson CA. Meckel-Gruber syndrome: an update on diagnosis, clinical management, and research advances. Front Pediatr. 2017;5:244. doi:10.3389/fped.2017.00244
15. Jaouad IC, Elalaoui SC, Sbiti A, Elkerh F, Belmahi L, Sefiani A. Consanguineous marriages in Morocco and the consequence for the incidence of autosomal recessive disorders. J Biosoc Sci. 2009;41(5):575–581. doi:10.1017/S0021932009003393