Distinction of Mohr’s Syndrome from OFD Type I: Case Report and Review of the Literature

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Abstract
The Oralfacialdigital Syndromes (OFD) results from the pleiotropic effect of a morphogenetic impairment affecting almost invariably the mouth, face and digits. In view of the different modes of inheritance and the different prognoses of the most common OFDs; OFD I, and II, it is important to establish a correct diagnosis in these patients. A case of type II OFD syndrome is being reported and the distinguishing clinico-radiological features with type I are compared. This case report also reviews the various other types of OFD and their distinguishing characteristics and emphasizes the early diagnosis and treatment of the same.

Key Words: Oralfacialdigital Syndrome, Mohr Syndrome, OFD1 Protein- Humann, Syndactyly, Brachydactyly, Genetics, X-Linked Disease, Gene CXORF5

Introduction
Oral-Facial-Digital Syndrome (OFD) is the collective name of a group of rare inherited syndromes characterized by malformations of the face, oral cavity, hands and feet [1]. Mohr is credited with the first description of patients with oral-facial-digital syndrome [2]. Although a case of apparent Mohr syndrome appears in the older literature (Case 460 of Otto monstrorum sexcentorum descriptio anatomica, 1841: Beckwith personal communication). Gorlin and Psamme published the first English report of the disorder with a detailed description [3]. Since then, several patients have been reported and at least 13 variants have been proposed. It is transmitted as an X-linked dominant/recessive trait. OFD VII, was withdrawn from the list because it was considered identical to OFD I [4].

Etiopathogenesis [5-8]
The cause of OFD I, a single mutation on gene CXORF5, the only one to have been identified to date. This gene is located on the short arm of the X chromosome (Xp22.3-22.2) and governs the codes for OFD syndrome protein I. This protein is essential for foetal survival and early development of all organs characteristically deformed in OFD [6]. The inheritance pattern of OFD I is X-linked dominant. Where most cases are caused by a new mutation in the gene, which occurs for the first time in the individual and is not inherited from either parent. The risk that parents of an affected child will have another child with the disease is therefore virtually non-existent. The new mutation, however, is hereditary and there is a risk that a woman with a new mutation will pass it down to the next generation through the X-linked dominant inheritance pattern. The gene responsible for OFD I: CXORF5, comprises of 23 exons encoding a 1011 amino acid protein (OFD1) that shares no sequence homologies with other proteins of known function [7]. Sub-cellular localization experiments showed that this protein is centrosomal and localized in the basal body of primary cilia. Interestingly, the OFD1 gene has been found to escape X-inactivation in humans, while the murine counterpart is subject to X-inactivation [7].

The inheritance pattern of OFD II is autosomal recessive, i.e. both parents are healthy carriers of the mutated gene (Figure 1). In each pregnancy involving the same partners, there is a 25% chance of the child inheriting the mutated gene from both parents. The child will then develop the disease. In 50% of cases the child will inherit only one copy of the mutated gene (from only one parent) and, like the parents, will become a healthy carrier of the mutated gene. In 25% of cases the child will inherit two normal genes and will neither develop the disease nor pass it on. If one parent is not a carrier, but the other has an inherited autosomal recessive disorder (and thus has two copies of the mutated gene), the children will all be carriers of the mutation but they will not have the disease. If an individual with an autosomal recessive disorder has a child with a partner who is a healthy carrier with one copy of the mutated gene, there is a 50% risk that the child will develop the condition, while in 50% of cases the child will be a healthy carrier of the mutated gene. OFD II is lethal for males. Most patients have been found to have normal chromosomal pattern [8].

Differential diagnosis
Acro–fronto–facio–nasal syndrome; Acrocallosal syndrome; Beemer-Langer syndrome; C syndrome; Carpenter syndrome; Craniofrononasal dysplasia; Egger-Joubat syndrome; Ellis-Van creveld syndrome; Grix syndrome; Holoprosencephaly–polydactyly syndrome; Jeune syndrome; Lemli-Opitz syndrome; Majewski syndrome; Pallister–Hall syndrome; and Smith- Short rib-polydactyly syndromes. For the majority of these conditions, except for Ellis-van creveld syndrome, Jeune syndrome, Pallister–Hall syndrome, and Smith-Lemli-Opitz syndrome, the responsible genes have not been identified yet and it is therefore impossible to make predictions as to whether some of them will end-up being allelic forms of OFDs.
**Diagnosis**
Once the clinician has ascertained a patient with OFD, any mode of inheritance or any positive family history should be ruled out. In patients with clear X-linked dominant transmission and in sporadic female patients, it is necessary to rule out mutations in the OFD1 gene. A brain MRI, an abdominal ultrasound, a skeletal survey, an ophthalmologic evaluation, and an audiometric test can differentiate different types of OFDs. A chromosome analysis should also be done to search for submicroscopic rearrangements by array-CGH analysis to obtain clues towards the identification of new candidate gene loci. OFD II is a rare autosomal recessive disease whose diagnosis is based only on clinical evidence. The molecular genetic basis is still unknown. And because of a variable clinical expression (even intra familial) the attribution of the correct diagnosis among the several forms of OFD is often difficult. OFD II appears to be much rarer than OFD I [9] and can be easily confused with OFD I. Therefore distinction between these two syndromes has important implications. Early accurate diagnosis is important for a genetic counseling point of view, since it implies a one in four risks of recurrence. Timely treatment and rectification is essential in providing the patient with a healthy lifestyle. We report a female patient with an amalgamation of anomalies similar to that observed by Mohr in 1941 suggestive of OFD type II.

**Case Report**
A 28 year old woman, the fourth child of a non-consanguineous 52 year-old mother and a late father (Figure 2) was referred to the Department of Periodontology, Dr. D.Y Patil Dental College & Hospital, Pune, India, for scaling of the teeth. With no history of OFD running in the family, this girl was born at full term, uneventful pregnancy, no prenatal and perinatal complications, weighed about 3200 gms. Past medical history revealed that she was admitted in the hospital one and a half years ago for swelling of lower limbs and face and was diagnosed with hypertrophic cardiomyopathy. Since then she has repeatedly complained of running nose. We compiled and reviewed all the clinical features of different Ofds (Table 1). As it is a case report and review of literature, no ethical clearance was required. However, the procedure of evaluation was explained, and written consent was obtained from the patient.

**Extraoral findings**
Sloping head, frontal bossing, broad nasal bridge ocular hypertelorism (Figure 2), syndactyly, brachydactyly, polydactyly (Figure 3), shortened hands, metaphyseal irregularity (Figure 3) and flaring and bilateral polydactyly of hallux (Figure 3).

**Intraoral findings**
As restricted mouth opening, multiple enlarged oral frenii (Figure 4) median cleft lip (Figure 2), cleft high arched palate (Figure 4), poly lobed tongue showing multiple hamartomas on the tongue, (Figure 5), hypoplasia of mandible (Figures 6 and 7), narrow maxillary arch partial anodontia crowding of teeth and posterior cross bite (Figure 5).

**Radiographic findings**
Radiograph of feet showed polydactyly and bilateral reduplicated hallux and skeletal deformities (Figure 7). Radiograph of hands shows duplication of right 1st and 4th Phalanges and triplication left 1st phalange (Figure 8).

**Investigations**
Blood Investigations revealed the following information: Hb 9.8 gms%, total WBC count 7900/cu.mm, slightly raised ESR 33 mm/hr. Other laboratory investigations revealed blood urea 25 mg/dl. Microscopic examination of the tongue biopsy showed multiple fingerlike projections of stratified squamous epithelium, normal cartilaginous tissue and minor salivary glands, hyperkeratinization with a central core of fibrovascular

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**Figure 1.** Inheritance pattern of OFD II.

**Figure 2.** A 28-year women, 4th child of a non-consanguineous. Note for median cleft lip, sloping head, frontal bossing and broad nasal bridge.
connective tissue. Audiometry revealed bilateral conductive hearing loss. A 46% hearing loss was reported.

**Treatment**
As observed this patient had a normal intelligence and thus can be successfully treated by multidisciplinary approach involving various plastic & reconstructive surgeries for clefts of the lip and palate; correction of tongue nodules & partial reduplication of the hallux; speech and language therapy; physiotherapy; orthopedics surgery for syndactyly and orthodontic therapy for maxillary arch expansion and correction of crowding; extraction of supernumerary teeth and frenectomies for correction of abnormal freni. A surgical attempt to reconstruct the auditory ossicles was advised to improve the conduction deafness.

A stepwise treatment was planned for this patient. Our treatment plan included initial phase-one therapy, (non-surgical periodontal therapy- scaling, root planning and polishing, oral hygiene instructions, 0.2% chlorhexidine mouthwash and modified Bass brushing technique was advised). A recall visit was scheduled after 4 weeks. Carious lesions were excavated and restored with either glass ionomer

<table>
<thead>
<tr>
<th>OFD Subtype</th>
<th>Synonym</th>
<th>OMIM</th>
<th>Inheritance pattern/Cause</th>
<th>Distinguishing feature</th>
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<tr>
<td>OFD I</td>
<td>Baraitser-Léage-Psaume syndrome [11]</td>
<td>311200</td>
<td>X-linked dominant Mutations in OFD1 gene CXORF5</td>
<td><strong>Oral:</strong> Micrognathia, median pseudo-clefting of upper lip &amp; palate, hyperplastic frenula, lobulated/bifid tongue, multiple hamartomas of the tongue [13,14] (in 70% cases of OFD [14]) thickened alveolar ridges and abnormal dentition, irregular margins of the lips. Facial: Partial asymmetry, frontal bossing, hypertelorism, hypoplasia of the maxillary bones and nasal alar cartilages, broadened nasal ridge, and vanishing cutaneous melia of the face and ears, (usually disappear before 3rd year of life) dryness, brittleness, and/or alopecia of the scalp hair, hypotrichosis. <strong>Digital malformations:</strong> [14] syndactyly, brachydactyly, clinodactyly, unilateral duplication of the hallux, and more rarely, pre- or postaxial polydactyly. <strong>CNS:</strong> [15] microcephaly, agenesis of corpus callosum [16] porencephaly, intracerebral epithelial or arachnoid cysts, heterotopia of gray matter, abnormal gyrations and mild mental retardation. <strong>Systemic:</strong> Polycystic kidney disease [16], pancreatic, ovarian and liver cysts [17]. Estimated incidence of 1:50,000–1:250,000 live births [6].</td>
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<tr>
<td>OFD II</td>
<td>Mohr/Mohr-Clausen Syndrome Syndrome [2]</td>
<td>252100</td>
<td>Autosomal recessive Mutations in unidentified gene.</td>
<td><strong>Oral:</strong> Midline clefts of the lip, thick frenula, multiple lingual hamartomas [14], micrognathia. <strong>Ocular:</strong> Dystopia, canthorum, ocular hypertelorism, <strong>Digital:</strong> Clinorachydactyly, syndactyly, and polysyndactyly of hallucles [8]. Conductive hearing impairment [15]. <strong>CNS:</strong> Porencephaly and hydrocephaly, CVS: atrioventricular canal and endocardial cushion defects.</td>
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<td>OFD III</td>
<td>Sugarman Syndrome [27]</td>
<td>258850</td>
<td>Autosomal recessive</td>
<td>Ceaseless seesaw winking of the eyes and/or myoclonic jerks, postaxial polydactyly, postaxial hexadactyly of hands and feet, profound intellectual disability, bulbous nose, low-set ears, lobulated hamartomatos of tongue, dental abnormalities, bifid uvula, pectus excavatum, short sternum, and kyphosis. Ceaseless seesaw winking of the eyes and/or myoclonic jerks. postaxial polydactyly, postaxial hexadactyly of hands and feet, profound intellectual disability, bulbous nose, low-set ears, lobulated hamartomatos of tongue, dental abnormalities, bifid uvula, pectus excavatum, short sternum, and kyphosis.</td>
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<tr>
<td>OFD IV</td>
<td>Baraitser-Burn Syndrome Syndrome [18,19]</td>
<td>258860</td>
<td>Autosomal recessive</td>
<td>Skeletal dysplasia, tibial dysplasia and polydactyly. The phenotypic spectrum has been subsequently expanded to include ocipitotischisis, brain malformation, ocular colobomas, intrahepatic cyst, renal cysts. Other findings include pectus excavatum, short stature anal atresia, rhizomelic limb defects (Severe tibial dysplasia differentiate type IV from type I) clinodactyly, unilateral duplication of the hallux, and more rarely, pre- or postaxial polydactyly, postaxial hexadactyly of hands and feet, profound intellectual disability, bulbous nose, low-set ears, lobulated hamartomatos of tongue, dental abnormalities, bifid uvula, pectus excavatum, short sternum, and kyphosis.</td>
</tr>
<tr>
<td>OFD V</td>
<td>Thurston Syndrome [20]</td>
<td>174300</td>
<td>Autosomal recessive</td>
<td>Polydactyly, postaxial, with median cleft of upper lip, early dental loss. Only one affected individual has had hyperplastic frenulae reported. Exclusively in Indian ethnic background [18].</td>
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<tr>
<td>OFD VI</td>
<td>Varadi-Papp Syndrome [21]</td>
<td>277170</td>
<td>Autosomal recessive</td>
<td>Polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation. cerebral and/or cerebellar malformations in endorganic gypsies (vermis hypoplasia/aplasia, Dandy–Walker anomaly) [20]. Hypothalamic hamartoma, cerebellar dysgenesis, absent pituitary gland with precocious puberty, penile agenesis and abnormal clavicles [22].</td>
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<tr>
<td>OFD VII</td>
<td>Whelan Syndrome [4,23]</td>
<td>608518</td>
<td>X-linked dominant</td>
<td>Hydronephrosis, Oral (tongue nodules, bifid tongue, midline cleft of the lip), facial (hypertelorism, alar hypoplasia), and digital abnormalities (clinodactyly), hydrencephaly and facial asymmetry.</td>
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<tr>
<td>OFD VIII</td>
<td>Edwards Syndrome [24]</td>
<td>300484</td>
<td>X-linked recessive</td>
<td>Bilateral preaxial and postaxial polydactyly, tibial and radial defects (short), and epiglottal abnormalities Hypertelorism or telecanthus, broad, bifid nasal tip, median cleft lip, tongue lobulation and/or hamartomas, oral frenula, high-arched or cleft palate, bilateral polydactyly, and duplicated hallucles.</td>
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<tr>
<td>OFD X</td>
<td>Figuera Syndrome [26]</td>
<td>165590</td>
<td>Autosomal recessive</td>
<td>Fibular aplasia, mesomelic limb shortening due to radial hypoplasia. Digital anomalies: oligodactyly and preaxial polydactyly</td>
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<td>OFD XI</td>
<td>Gabrielli Syndrome [27]</td>
<td>-</td>
<td>Autosomal recessive</td>
<td>Craniovertebral anomalies, ventriclemegaly, microcephaly, apophysis, fusion of vertebral arches in C1, C2, and C3, and clefts of vertebral bodies in a sporadic male patient, postaxial polydactyly, alar hypoplasia, duplicated vomer, midline cleft involving palate, vomer, ethmoid and crista galli</td>
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<tr>
<td>OFD XII</td>
<td>Moran Barroso Syndrome [28]</td>
<td>-</td>
<td>Autosomal recessive</td>
<td>Myelomeningocele, stenosis of the aqueduct of Sylvius, Dysplasia of AV valves</td>
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<tr>
<td>OFD XIII</td>
<td>Degner Syndrome [29]</td>
<td>-</td>
<td>Autosomal recessive</td>
<td>Psychiatric symptoms (major depression), epilepsy and leukoaraiosis (brain MRI) in association with core oral, facial, and digital findings.</td>
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Figure 3. Syndactyly, brachydactyly, polydactyly of hands & feet, shortened hands, bilateral polysyndactyly of hallux, and metaphyseal irregularity.

Figure 4. High arched cleft palate and narrow maxillary arch, restricted mouth opening and multiple enlarged oral frenii.

Figure 5. Poly lobed tongue showing multiple hemartomas, narrow maxillary arch, partial anodontia, crowding of teeth and posterior crossbite.

cement or composites. Grossly destructed teeth were extracted and endodontic therapy was rendered for restorable teeth with stainless steel crowns. As hyperactive mobility of the tongue was concerned, only fixed prosthesis were given. Frenectomy...
Interdisciplinary approach included correction of cleft lip and palate in the department of Oral and Maxillofacial surgery. Orthodontic expansion of the narrow arch and fixed orthodontic appliances for the correction of the mal-aligned teeth and posterior cross-bite are carried out simultaneously. Orthodontic therapy is still to be completed and the patient is on monthly recalls. Growth and development of face and jaws are being monitored along with regular follow-up for assessment of speech. Management of this case was made according to the guidelines treatment and management of OFD 1 [1,5].

**Discussion**

Mohr [2] in 1941 described a family in which male proband had OFD malformation including a high arched palate, lobulate tongue, with papilliform outgrowths, a broad root of nose, ocular hypertelorism, syndactyly, brachydactyly and polydactyly of hands and feet. Important characteristic feature was polysyndactyly of the great toes. The reported child had three brothers who had more limited malformations of oral cavity and digits. Mohr concluded that this syndrome was due to a sex linked recessive sublethal gene [2]. Later Claussen [10] in 1946 reported a similarly affected child born to consanguineous parents of the same family reported by Mohr, thus leading to the conclusion that the syndrome was inherited as an autosomal recessive trait. A similar syndrome was described by Papillon-Leage and Psaume [11] who recognized that the condition was hereditary and affected exclusively females. Subsequent reports of only females with this OFD phenotype strengthened the hypothesis that it was inherited as an X-linked dominant trait. This hypothesis was confirmed almost 50 years later when Ferrante et al. unraveled the genetic basis in 2001 [7]. For some unknown reason, all subsequent literature reports referred to the X-linked dominant form (Papillon-Leage and Psaume) and not the X-linked recessive form (Mohr). Thus as a general consensus as X-linked dominant was excepted as OFD I, even though it...
was described after the recessive form of Mohr and Claussen, which is now referred to as OFDS II. After the description of OFD I and II, the phenotypic spectrum was further expanded with extra-OFD manifestations [12] leading to the definition of new types, each being characterized either by distinctive clinical findings and/or by a specific mode of inheritance. Till date, about 13 variants have been proposed [13].

**References**


**Conclusion**

Mohr syndrome (OFD II) appears to be much rarer than OFD I. It can be easily confused with OFD I. Therefore early distinction between these two syndromes has important implications in genetic counseling.

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