Review

Human facial dysostoses

The human facial dysostoses can be subdivided into mandibulofacial dysostoses (MFDs) and acrofacial dysostoses (AFDs). The craniofacial phenotypes of the two groups of patients are similar. Both types are thought to be related to abnormal migration of neural crest cells to the pharyngeal arches and the face. The craniofacial anomalies shared by the two groups consist of downslanting palpebral fissures, coloboma of the lower eyelid, from which the eyelashes medial to the defect may be absent, hypoplasia of the zygomatic complex, micrognathia, and microtia, which is often associated with hearing loss. These facial deformities are associated with limb anomalies in the AFDs. All MFDs present with the typical craniofacial phenotype, but some have additional features that help to distinguish them clinically: intellectual disability, microcephaly, chest deformity, ptosis, cleft lip/palate, macroblepharon, or blepharophimosis.

The limb anomalies in the AFDs can be classified into pre-axial, post-axial, and others not fitting into the first two AFD types. Of the pre-axial types, Nager syndrome and of the post-axial types, Miller syndrome are the best-known disorders of their AFD subgroups. Several other AFDs with unknown molecular genetic bases, including lethal ones, have been described. This article reviews the MFDs and AFDs published to date.

Conflict of interest

The author declares no conflict of interest.

The development of structures derived from the first and second branchial arches is disturbed in the human facial dysostoses. This heterogeneous group of conditions can be subdivided into those with normal extremities, the mandibulofacial dysostoses (MFDs), and those with limb anomalies, the acrofacial dysostoses (AFDs).

For diagnostic convenience, schematic overviews of MFD and AFD are depicted in Figs 1 and 2, respectively. It should be mentioned that this review includes single cases of MFDs and AFDs, although it is still unclear whether each of them truly represents a distinct syndromic condition.

Mandibulofacial dysostoses

At least eight different types of MFD have been described in the literature (Table 1), and one can expect that their number will rise in the coming years. One has to keep in mind that many of the clinically defined MFDs were described before the causative genes, e.g. Treacher Collins syndrome (TCS), were identified. As the different forms of MFD overlap considerably, some of these patients may need to be reclassified after the molecular bases of their malformations have been determined. As long as molecular data to the contrary are not available, these entities will be listed as distinct MFDs.

The craniofacial anomalies observed in the MFDs result from faulty development of the first and second branchial arches. The MFDs are characterized by downslanting palpebral fissures, coloboma of the lower eyelids with or without the absence of eyelashes on the affected lids medial to the defect, hypoplasia of the zygomatic complex, retrognathia, and microtia, which is often associated with hearing loss. The craniofacial features show wide intrafamilial and interfamilial variability.

All the MFDs described so far have been published independently. To the best of our knowledge, a review of the subclassification of MFDs does not exist.
presents an MFD classification based on clinical findings and the common craniofacial phenotype.

Treacher Collins syndrome (MIM 154500)

The best-known MFD is the TCS, which was first described by Thomson in 1846 and Berry in 1889. It is named after E. Treacher Collins, who delineated this syndrome in 1900. For an excellent review, see Ref. (1). Two further subtypes of TCS, TCS2 (MIM 613717) and TCS3 (MIM 248390), were described in 2011. One of them, TCS3, is inherited in an autosomal recessive manner (2).

TCS1, an autosomal dominant disorder with reduced penetrance, is usually characterized by symmetric craniofacial anomalies consisting of downslanting palpebral fissures (all of 35), coloboma of the lower eyelids (19 of 35) with absent eyelashes medial to the defect, hypoplasia of the zygomatic bones (34 of 35), variable microtia (25 of 35) often with atresia of the external ear canals (23 of 34), and micrognathia (32 of 35) (3). A patient showing the typical deformities is shown in Fig. 3. Intellectual ability is usually normal. TCS1 occurs in 1:50,000 live births.

Mutations of the TCOF1 gene, which is localized in 5q32-q33.1 and encodes the nucleolar phosphoprotein Treacle, are causative of TCS (4). About 60% of the mutations have occurred de novo in the index patients. The heterozygous, mostly truncating mutations are scattered throughout the gene. There is no obvious genotype–phenotype relationship. In a mouse model for TCS, Dixon et al. (5) showed that haploinsufficiency of Tcof1 leads to defects in migration of neural crest cells, which result in severe craniofacial malformations. It was hypothesized that Treacle regulates proliferation by controlling the production of mature ribosomes. Thus, Treacle is assumed to be a regulator of ribosome biogenesis.

Very recently, partial TCOF1 gene deletions have been identified as being causative of TCS in a subset of patients (6, 7).

In 2011, two further genes, POLR1D and POLR1C, were reported to be the causative of TCS2 and TCS3, respectively (2). Those genes encode subunits of RNA polymerases I and III, and both polymerases are involved in ribosomal RNA transcription. Twenty heterozygous POLR1D mutations were identified in patients with TCS with wide clinical variability, and non-penetration was observed. In addition, three families with compound heterozygous POLR1C mutations have been described. It was assumed that TCS3 follows an autosomal recessive mode of inheritance.

MFD type Hutterite (MIM 248390)

This type of MFD is listed in Online Mendelian Inheritance in Man (OMIM) as type 3 TCS, although no POLR1C mutation results have been reported for this family. Lowry et al. (8) described two affected sisters born to apparently unaffected consanguineous parents. The craniofacial features of the two sisters closely resemble those of TCS, with malar and mandibular hypoplasia, downslanting of the palpebral fissures, lower eyelid coloboma with lack of eyelashes medial to the defect, dysplastic ears, and conductive hearing loss. The family was described before the causative genes of TCS were identified. Although the parents are consanguineous, thus making autosomal recessive inheritance likely, one cannot exclude that the MFD of these sisters follows an autosomal dominant inheritance pattern with reduced penetrance or germline mosaicism in one of the parents.

There is one MFD with intellectual disability (ID) and microcephaly: MFD type Toriello. AFD type Guion-Almeida, formerly known as an MFD with microcephaly or MFD type Guion-Almeida, was reclassified as a pre-axial AFD because many of these patients presented with thumb anomalies.

MFD type Toriello (MIM 301950)

This MFD was described in 1985 (9) as a most probably X-linked branchial arch syndrome in three boys – two
Fig. 2. Classification of acrofacial dysostoses (AFDs). Clinical findings characterizing the different forms of AFDs are shown. The subgroups are differentiated into pre-axial (blue), post-axial (orange) and other (green), which does not fit into the first two groups. ID, intellectual disability; GU, genitourinary; CHD, congenital heart defects; extr., extremities; phal., phalangeal; rectovag., rectovaginal; synd., syndactyly; ret, retarded.
Table 1. Classification of mandibulofacial dysostoses

<table>
<thead>
<tr>
<th>Subtype</th>
<th>OMIM</th>
<th>Inheritance pattern</th>
<th>Protein</th>
<th>Gene</th>
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<tbody>
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<td>Treacle</td>
<td>TCOF1</td>
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<td>613717</td>
<td>AD</td>
<td>Polymerase (RNA) I polypeptide D, 16kDa</td>
<td>POLR1D</td>
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<tr>
<td>Treacher Collins syndrome type III</td>
<td>248390</td>
<td>AR</td>
<td>Polymerase (RNA) I polypeptide C, 30kDa</td>
<td>POLR1C</td>
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<td>248390</td>
<td>Uncertain</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MFD type Toriello</td>
<td>301950</td>
<td>XR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MFD type Hedera-Toriello-Petty</td>
<td>608257</td>
<td>AD</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MFD type Bauru</td>
<td>604830</td>
<td>AD</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MFD type Verloes</td>
<td>602562</td>
<td>Uncertain</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MFD type Zhang</td>
<td>–</td>
<td>Uncertain</td>
<td>Duplication 1p36.33 and duplication 1q21.2q22</td>
<td>–</td>
</tr>
<tr>
<td>Burn-McKeown syndrome</td>
<td>608572</td>
<td>Uncertain</td>
<td>–</td>
<td>–</td>
</tr>
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</table>

AD, autosomal dominant; AR, autosomal recessive; MFD, mandibulofacial dysostoses; OMIM, Online Mendelian Inheritance in Man; XR, X-chromosomal recessive.

Fig. 3. A girl aged 13 years 6 months presenting with Treacher Collins syndrome due to a TCOF1 mutation [same as patient M17995 in Ref. (3)].
(a) The characteristic facial appearance with hypoplasia of the zygomatic bones and mandible, downslanting palpebral fissures, coloboma of the lower eyelids with absent eyelashes medial to the defect, and large mouth. (b) Side view shows a convex profile of her face with receding forehead and retromicrognathia, downslanting palpebral fissures and third-grade microtia.

MFD type Hedera-Toriello-Petty (MIM 608257)

The MFD type Hedera-Toriello-Petty is characterized by the presence of ptosis. This MFD, described in a single family, followed an autosomal dominant inheritance in four affected generations (13). This form of MFD did not show linkage to the TCOF1 gene region in 5q32. The main and variable clinical findings were ptosis, hypoplasia of the zygomatic arch, micrognathia, malocclusion, and malformed ears. The face was asymmetric in some cases, then resembling oculo-auriculo-vertebral spectrum (OAVS)/Goldenhar syndrome. No causative gene has been described so far.

MFD type Bauru (MIM 604830)

Cleft lip/palate is the discriminating clinical sign in MFD type Bauru. Only one autosomal dominant family and one single patient with this type of MFD have been described (14, 15) by Marcano and Richieri-Costa and by Zechi-Ceide and Guion-Almeida. These patients presented with malar and mandibular hypoplasia, cleft lip with or without cleft palate, mild upslanting palpebral fissures, and abnormal ears. The authors state that this MFD is distinct, differing from the known MFDs. Mutation analysis of the known MFD genes in these patients has not been performed so far, and the causative gene is unknown.
MFD type Verloes (MIM 602562)

Verloes and Lesenfants reported a girl with MFD, macroblepharon and macrostomia (MIM 602562) (16). She had a round, flat face, marked hypertelorism, downslanting palpebral fissures, anteverted nares, small ears, a large mouth, and retrognathia, and had normal intelligence. Macroblepharon helps to distinguish this condition from the other MFDs. There is some overlap before the MFD type with Kabuki syndrome, but the patient was reported before the MLL2 gene, causative of Kabuki syndrome, was identified.

MFD type Zhang

Zhang et al. (17) described a newborn female with MFD, microtia, and limb anomalies without specific limb defects, but described claw-like hands and club feet. The hand or foot anomalies are not clearly visible on the photographs. However, she had de novo microduplications in 1p36.33 (a 722-kb duplication containing 51 genes) and in 1q21.3-q22 (136-kb duplication containing 12 genes). The authors suggest that two of the duplicated genes, VWA1 and PYGO2, are good candidates for causing the disease. VWA1 plays an important role in cartilage structure and function, and PYGO2 in the Wnt transduction pathway. So far, no further patients have been described with this phenotype and duplication of these regions. No data of mutation screening for these genes in MFD patients are available. Thus, the significance of the duplicated genes remains unclear.

Burn-McKeown syndrome (MIM 608572)

In 1992, Burn et al. described five children (two pairs of brothers and one isolated female patient) from three families with bilateral choanal atresia, cardiac defects, hearing loss, protruding external ears, and coloboma of the eyelids (18). In the female patient, a de novo ring chromosome 18 was identified: 46,XX,r(18)(p14q23). Two subsequent reports of this syndrome (19, 20) did not confirm chromosome 18 aberrations. However, the craniofacial phenotype with narrow palpebral fissures, coloboma of the eyelids, high nasal bridge, and an expressionless face should be an easily recognizable constellation of Burn-McKeown syndrome that appears to be recognizable, although there is some overlap with TCS. In 2006, Hing et al. (21) described a large consanguineous Alaskan family with choanal atresia, cleft lip/palate, small cup-shaped ears, mixed hearing loss, and preauricular tags. They named it oculo-oto-facial syndrome (MIM 610332). It is still an open debate whether Burn-McKeown syndrome and oculo-oto-facial syndrome are different manifestations of the same disorder as there is considerable clinical overlap (22). This will be resolved as soon as the genetic cause of this condition is identified.

Acrofacial dysostoses

A review of the literature revealed that at least 18 different forms of AFDs have been described (Table 2; Fig. 2). One can subdivide these entities into those with pre-axial involvement of the extremities, those with post-axial involvement, and those with limb anomalies not fitting into the first two groups.

### Table 2. Classification of acrofacial dysostoses

<table>
<thead>
<tr>
<th>Subtype</th>
<th>OMIM</th>
<th>Inheritance pattern</th>
<th>Protein</th>
<th>Gene</th>
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<tbody>
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<td>Nager syndrome</td>
<td>154400</td>
<td>AD</td>
<td>U2SNP</td>
<td>SF3B4</td>
</tr>
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<td>AFD type Guion-Almeida</td>
<td>610536</td>
<td>AD</td>
<td>U5 snRNP-specific protein, 116 kDa</td>
<td>EFTUD2</td>
</tr>
<tr>
<td>AFD type Kennedy-Teebi</td>
<td>–</td>
<td>AR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AFD type Kelly</td>
<td>–</td>
<td>AR/XR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AFD type Reynolds</td>
<td>–</td>
<td>AD</td>
<td>Microdeletion 16p13.3?</td>
<td>–</td>
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<tr>
<td>Miller (Genée-Wiedemann) syndrome</td>
<td>263750</td>
<td>AR</td>
<td>Dihydroorotate dehydrogenase</td>
<td>DHODH</td>
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<td>AFD with vertebral defects</td>
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<td>Uncertain</td>
<td>–</td>
<td>–</td>
</tr>
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<td>Weyers acrofacial dysostosis</td>
<td>193530</td>
<td>AD</td>
<td>EVC2</td>
<td>EVC2</td>
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<td>AFD type Arens/Tel Aviv</td>
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<td>Rodriguez</td>
<td>201170</td>
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<td>AFD severe post-axial type</td>
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<td>Uncertain</td>
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<td>AFD type Bates</td>
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<td>AFD type de Macena Sobreira</td>
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<td>Uncertain</td>
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<tr>
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<td>DLX5/6?</td>
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<td>AFD type Palagonia</td>
<td>601829</td>
<td>AD</td>
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</table>

AD, autosomal dominant; AFD, acrofacial dysostoses; AR, autosomal recessive; OMIM, Online Mendelian Inheritance in Man; POADS, postaxial acrofacial dysostosis syndrome; XR, X-chromosomal recessive.
ears in 18 of 20 (90%) associated with hearing loss in 24 (96%), abnormal palate in 15 of 22 (68%), dysplastic lower eyelashes in 6 of 14 (43%), micrognathia in 23 of 26 (88%). Fissures were present in 20 of 21 (95%) patients, absent history of Nager syndrome. Downslanting palpebral phenotype: 15 were sporadic, without a positive family mutation-positive patients with a characteristic Nager syndrome occurring in siblings born to unaffected parents (30). Either an autosomal recessive form exists, or the disorder shows reduced or non-penetrance, or there is germine mosaicism in the parents. Three AFDs with ID have been delineated: AFD type Guion-Almeida, type Kennedy-Teebi, and type Kelly.

Pre-axial AFDs

Nager syndrome (MIM 154400)
The best-defined pre-axial dysostosis syndrome is the Nager syndrome (23), first described by Nager and DeReynier in 1948 (24). It is characterized by craniofacial anomalies consisting of downslanting palpebral fissures, malar hypoplasia, micrognathia, external ear anomalies leading to conductive deafness, and cleft palate. The pre-axial limb anomalies are very variable and often asymmetric. The thumb anomalies include hypoplasia or aplasia of the thumb, duplicated thumb, limited movement of the thumb, and symphalangism (Fig. 4). Radial hypoplasia or ahypoplasia is often associated with proximal radioulnar synostosis. Lower limb involvement is usually mild and rare: talipes, hypoplastic hallux and other toes, and absence of creases at the toes. Associated internal malformations are also rare. The incidence of Nager syndrome appears to be low, with an estimate of 3/1,000,000 in Finland (25). Fewer than 100 patients have been described. Convincing autosomal dominant and autosomal recessive families have been described. Thus, there might be genetic heterogeneity.

In 2012, haploinsufficiency of SF3B4 was shown to be the causative of Nager syndrome in half of the patients (20 of 35) fitting this diagnosis by an international collaboration using exome sequencing (26). This gene encodes a component of the U2 pre-mRNA spliceosomal complex, which belongs to the major spliceosome. Bernier et al. (26) described 26 mutation-positive patients with a characteristic Nager phenotype: 15 were sporadic, without a positive family history of Nager syndrome. Downslanting palpebral fissures were present in 20 of 21 (95%) patients, absent lower eyelashes in 6 of 14 (43%), micrognathia in 23 of 24 (96%), abnormal palate in 15 of 22 (68%), dysplastic ears in 18 of 20 (90%) associated with hearing loss in 19 of 20 (95%), radial ray anomalies in 10 of 17 (59%), abnormal thumbs in all of 22, radioulnar synostoses in 15 of 18 (83%), and delayed development in 6 of 12 (50%) patients. Bernier et al. stated that the mutation-negative patients had similar clinical findings, making it impossible to differentiate between mutation-positive and mutation-negative patients on clinical grounds alone. To the best of our knowledge, only one patient with Nager syndrome and a deletion comprising the whole SF3B4 gene has been described (27). No partial gene deletions or duplications have been described so far. It is assumed that spliceosomes directly regulate developmental genes by the control of splicing or tissue specificity (26). Thus, Nager syndrome could be caused by the aberrant splicing of genes involved in limb and craniofacial development. However, it is also known that SAP49, the protein encoded by SF3B4, inhibits BMP-mediated osteochondral cell differentiation (28).

Our own group investigated 12 further patients with Nager syndrome and found truncating SF3B4 mutations in 7 of them (29). This is in agreement with the data from Bernier et al., who also found mutations in half of the patients. Although gross deletions or duplications of SF3B4 were not excluded in the remaining patients, one can assume that Nager syndrome is a heterogeneous disorder.

There are a few reports in the literature of Nager syndrome occurring in siblings born to unaffected parents (30). Either an autosomal recessive form exists, or the disorder shows reduced or non-penetrance, or there is germine mosaicism in the parents.

AFD type Guion-Almeida (MIM 610536)
In 2006, Guion-Almeida et al. described two new and two previously described patients (31) with growth retardation and ID, MFD, microcephaly, and cleft palate. They proposed that this condition is a new syndrome (32) (MIM 610536). Three years later, Wieczorek et al. described three unrelated, sporadic patients with the main clinical findings of MFD consisting of lower eyelid coloboma, dysplastic ears, micrognathia, cleft palate, and deafness. In addition, the patients had ID, microcephaly, and choanal atresia. They also proposed that the patients represent a new, previously undescribed condition distinct from the known MFDs (33). Exome sequencing to identify the causative gene and molecular analyses of the patients showed that these patients had the same distinct MFD (Fig. 5). In 2012, the EFTUD2 gene was shown to cause this autosomal dominant condition (34). The mutations occurred throughout the gene; a partial deletion of the gene and a complex rearrangement were also identified. The mutations are compatible with haploinsufficiency. The EFTUD2 gene (elongation factor Tu GTP-binding domain-containing 2) encodes for the U5-116 kDa protein, one component of the major spliceosome. It occupies a central position within the U4/U6-U5 tri-snRNP particle. Considering that splicing

Fig. 4. A 4-year 5-month-old patient with typical Nager syndrome presenting with slightly downslanting palpebral fissures, severe micrognathia and tracheostoma. Hands show oligodactyly after policization.
is an obligatory process for gene expression in all cells, the unresolved question is why \textit{EFTUD2} mutations lead to a complex multiple malformation syndrome with ID, whereas mutations in genes encoding other spliceosomal subunits (hBrr2, hPRP8, hPRP6, and hPRP31) only produce retinitis pigmentosa, a result of the tissue-specific death of photoreceptor cells. An excellent review on the function of the spliceosome was published by Wahl et al. (35).

All 12 sporadically occurring patients with an obviously very similar and distinct phenotype included in this study carried a mutation. The common clinical findings were ID (all of 12), small for gestational age (3 of 12), prenatal-onset microcephaly (6 of 8) and postnatal microcephaly (all of 12), midline cleft palate/bifid uvula (7 of 12), choanal atresia (6 of 10), congenital heart defect (7 of 12), and anomalies of the thumbs (5 of 12). Because half of the patients with this condition known as MFD type Guion-Almeida have thumb anomalies, they should be reclassified as AFD type Guion-Almeida. Two further patients with \textit{EFTUD2} mutations were found in a group of 12 probands with unexplained syndromes (36) who were examined by exome sequencing. The authors concluded that their patients had similarities with the patients showing MFD and microcephaly described by Lines et al. (34). A third patient previously diagnosed with Nager syndrome was described by Bernier et al. (26). This patient and 5 of the 12 patients described by Lines et al. also had thumb anomalies, namely hypoplasia or duplication of thumbs, therefore overlapping with Nager syndrome patients. The microcephaly in AFD type Guion-Almeida, which is usually absent in Nager syndrome, might help to distinguish these conditions.

In addition, mutations in \textit{EFTUD2} are also causative of a type of syndromic esophageal atresia (EA), namely AFD with EA or OAVS associated with EA (37). Gordon et al. identified 10 patients with \textit{EFTUD2} deletions or mutations; of which 8 patients presented with EA. Thus, phenotypes caused by \textit{EFTUD2} mutations are important in the differential diagnoses of CHARGE and Feingold syndromes. Another article, published by Luqueti et al. (38), expanded the phenotypic spectrum of individuals with \textit{EFTUD2} mutations to include epibulbar dermoids and clefting of the zygomatic arch. They recommend that individuals with features of OAVS and bilateral microtia should probably be tested for \textit{EFTUD2} mutations. One of their patients with an \textit{EFTUD2} mutation did not have microcephaly, indicating that the phenotype of patients with \textit{EFTUD2} mutations is highly variable. Furthermore, in a family with EA and microtia described by Wieczorek et al. (39), in which the two affected siblings and their mother were shown to have an \textit{EFTUD2} splice site mutation, the clinically suspected mosaicism of their mildly affected mother could not be molecularly proven (own unpublished data). This shows that the phenotypic spectrum is wide with very mildly affected mutation carriers.

**AFD type Kennedy-Teebi**

A probably autosomal recessive form of AFD was first described by Kennedy and Teebi (40) in two patients; another possible case was described in 2005 (41). The patients’ phenotypes, including those of a sister–brother
pair, overlapped somewhat with that of Nager syndrome, but included the following distinguishing features: microcephaly, cleft palate, beaked nose, blepharophimosis, and developmental delay.

AFD type Kelly
Three male siblings described by Kelly et al. (42) had mild AFD with hearing loss, mild ID, short stature, and genitourinary anomalies consisting of hypospadias and undescended testes. The boys had symphalangism of the thumbs and the interphalangeal joints of the index finger. No further patients with this condition have been described. Autosomal recessive inheritance was suggested, but X-linked inheritance cannot be excluded.

AFD type Reynolds
One pre-axial AFD without ID has been described by Reynolds et al., who described an autosomal dominant form of AFD in 1986. Two subsequent articles confirmed that such an autosomal dominant subtype of AFD exists (43–45). The patients have mild MFD (prominent forehead, ptosis, downsloping palpebral fissures, malar hypoplasia, highly arched palate, and micrognathia) and anomalies of the first ray. They closely resemble patients with Nager syndrome. Dauwerse et al. described an adult patient with clinical signs of AFD type Reynolds, who also had tuberous sclerosis and autosomal dominant polycystic kidney disease (45). He was shown to have a TSC2-PKD1 contiguous gene syndrome with a microdeletion in 16p13.3. As the patients reported by Reynolds et al. did not display features of tuberous sclerosis and autosomal dominant polycystic kidney disease, the significance of the 16p deletion remains unclear.

Post-axial AFDs
Only four post-axial AFDs have been described until now. They are clinically delineated by post-axial involvement of limbs and the associated anomalies. Besides the Miller syndrome, which is very distinct, one post-axial AFD includes vertebral defects, one includes ectodermal involvement (AFD type Weyers), and one includes syndactyly of the fingers (AFD type Arens).

Miller syndrome (MIM 263750)
Miller syndrome [Genée-Wiedemann, Wildervank-Smith, and postaxial acrofacial dysostosis syndrome (POADS)], the best known and best understood post-axial AFD, was first described by Genée (46) in 1969, Wiedemann (47) in 1973, and Miller et al. (48) in 1979. With only about 30 articles having been published on this condition, it appears to be rare. Patients are characterized by craniofacial dysmorphism and symmetric post-axial limb anomalies with hypoplasia or aplasia of the (fourth and) fifth ray affecting the upper and lower limbs. Hypoplasia of ulna and radius may be present. Intelligence is usually normal. This autosomal recessive condition was the first entity resolved by exome sequencing (49) in four affected individuals of three independent kindreds. Filtering led to the identification of a single candidate gene, DHODH, in each of the four patients. This gene encodes a key enzyme, dihydroorotate dehydrogenase, in the pyrimidine biosynthesis pathway.

Additional clinical, molecular, and detailed functional data on DHODH were described recently (50, 51). It was shown that those patients with mutations within DHODH display a very characteristic phenotype, whereas those without mutations had involvement of upper or lower limbs only or they had pre-axial anomalies in addition to the post-axial ones. In addition, patients with DHODH mutations presented with craniofacial dysmorphism consisting of micrognathia (all of 5), orofacial clefts (4 of 5), malar hypoplasia (all of 3), eyelid coloboma (1 of 4) and ear dysplasia (3 of 4). Four of five patients had bilateral absence of the fifth ray of the hands and all of 5 of the feet. No mutations were identified in the other pyrimidine biosynthesis genes (CAD and UMPS) in those patients with Miller syndrome without DHODH mutations. One typical, mutation-carrying patient with Miller syndrome is depicted in Fig. 5. No patient with Miller syndrome carries homozygous mutations, and truncating mutations are rare. Thus, the molecular mechanism underlying Miller syndrome might be atypical (50), Rainger et al. (50) found that two patients with DHODH mutations had elevated levels of orotic acid but not of dihydroorotate in their urine.

Post-axial AFD and vertebral defects
This condition was described by Medeira and Donnai in a single male fetus (52). He had MFD with cleft lip and palate and both ears were absent. The fifth digit was hypoplastic on one hand and aplastic on the other hand. In addition, he had scoliosis and talipes equinovarus. Radiographs showed multiple cervical and thoracic hemivertebrae. The mode of inheritance is unclear.

Weyers AFD (MIM 193530)
This autosomal dominant condition was first described by Weyers in 1952 (53). It is characterized by post-axial polydactyly, dysplastic nails, oligodontia, and enamel hypoplasia. In the meantime, several patients with this condition have been described. The causative genes, EVC and EVC2, localized in 4p16 (54), are in 5’ to 5’ head-to-head orientation close to transcription start sites (55). Weyers AFD is allelic to the autosomal recessive Ellis van Creveld syndrome. The latter is a skeletal dysplasia with clinical signs that overlap with those of Weyers AFD but includes additional features such as disproportionate dwarfism, thoracic dysplasia, and congenital heart disease (54). Both genes are responsible for the basal body of the cilia, leading to the assumption that Weyers AFD belongs to the group of ciliary disorders (55). Three heterozygous mutations have been identified in Weyers AFD, all localized in exon 22 of EVC2.
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**AFD type Arens or Tel Aviv**

This condition has been described in a single girl only (56). The affected girl was born to unaffected consanguineous parents. She presented with MFD (hypertelorism, downslanting palpebral fissures, low-set ears, micrognathia, and small mouth) and absence of the fifth ray on all extremities. In addition, she displayed syndactylies on both hands, bilateral congenital hip dislocation, and club feet. The distal phalanges of the second and third toes were absent. The mode of inheritance is unknown.

**Other AFDs**

This group contains those types not fitting into the preaxial or postaxial AFDs. Four of these AFDs are lethal: AFD type Rodríguez, severe AFD, AFD type Bates, and AFD de Macena Sobreira. Another type belonging to this group is AFD type Karaman-Kavecci, characterized by hypoplasia of the ulna, femur, and fibula. In addition, there is a group of post-axial AFDs with ID (AFD type Patterson-Stevenson, Catania, and Richieri-Costa-Pereira) and one type with oligodontia, frizzy hair, and short stature (AFD type Palagonia).

**AFD type Rodríguez (MIM201170)**

In 1990, Rodriguez et al. described three male sibs with a distinct form of AFD and unaffected parents (57). The sibs had facial dysostosis with severe mandibular hypoplasia leading to neonatal death due to respiratory complications. The upper limbs were severely shortened, with hypoplasia of humerus and synostotic formation of the lower forearms. The fifth rays were lacking in the hands and/or feet. The hand anomalies were variable with additional anomalies of the fourth ray, syndactyly of the first and second fingers, hypoplastic thumbs, and syndactyly of the fourth and fifth rays. In addition, two of the three patients had congenital heart defects, including atrial septal defect, ventricular septal defect, pulmonary atresia, and overriding aorta. Arhinencephaly was also reported. Further such cases, including females, have been described, confirming that this may be a distinct autosomal recessive entity (57). The gene is still unknown. For a detailed review of this disorder, see Ref. (58).

**AFD severe post-axial type**

In 1990, Rodriguez and Palacios (59) described a single female stillborn infant as a severe case of POADS. The infant had features of MFD with maxillary, mandibular, and malar hypoplasia, low-set and malformed ears, broad nasal bridge, and a coloboma of the lower eyelid. The limb anomalies were severe with shortening of the limbs, bilateral syndactyly with synostosis of the fourth and fifth fingers, and a hypoplastic left thumb. Additional anomalies included hypoplastic scapulae, short and broad clavicles, supernumerary cervical vertebrae, absence of the ulnae, and bowed radii. The lower limbs were also short and bowed. There was a short third toe and syndactyly of the fourth and fifth toes.

Further cases were described by Poissonnier et al. (60) and Stephan (61). The genetic cause is still unknown.

**AFD type Bates**

This type of severe AFD also appears to be very rare. It was described in a single female fetus (62) born to unaffected consanguineous parents. The fetus showed MFD (hypertelorism, downslanting palpebral fissures, ectropion of lower eyelids, absence of lower eyelashes, micrognathia, cleft lip/palate, and severe microtia). The limbs were severely shortened and bowed. There was oligodontaly of the hands and feet, with three fingers and four toes bilaterally. X-rays showed shortening of the ulnae, short and bowed radii, and dislocation at the elbow joint. Three metacarpals were present in both hands. The distal phalanges of the thumbs were duplicated, as were the distal two phalanges of the third digits. Tibiae and fibulae were shortened. The feet had four metatarsals. Internal malformations consisted of bilateral renal agenesis and bicornuate uterus. The mode of inheritance is unknown.

**AFD type de Macena Sobreira**

This type of AFD, associated with frontonasal dysplasia, was described in a single stillborn infant only (63). The infant had a prominent forehead, severe hypertelorism, absent nose, macrostomia with bilateral cleft
lip/palate, micrognathia, and low-set ears. The upper limbs were short with shortened radii and radioulnar and ulnarhumeral synostoses. The fibulae were bilaterally absent. Ptterygia were present at the elbows and knees. Brachyactyly of the hands and feet was also present. Internal malformations included microphthalmia, small kidneys, rectal atresia with rectovaginal fistula, posteriorly rotated vagina, and absent anus. There was some overlap with AFD type Rodriguez, but this fetus had additional malformations: frontonasal dysplasia with absence of the nose and rhinencephalon. The causative gene and mode of inheritance are still unknown.

**AFD type Karaman and Kahveci**

This type is characterized by shortening of the long bones, namely the ulna, femur, and fibula. Karaman and Kahveci (64) described a newborn male with micrognathia, mid-face hypoplasia, radio-humeral synostosis, hypoplasia of the left radius, the left femur, the right fibula, and of the ulna bilaterally. This condition appears to differ from the other AFDs. As only a single patient was described, the mode of inheritance is unclear.

**AFD type Patterson-Stevenson-Fontaine (MIM 183700)**

ID is the specifiable clinical sign in the AFD types Patterson-Stevenson, Catania, and Richieri-Costa-Pereira. This form of AFD was first described by Patterson and Stevenson in 1964 as a craniofacial dysostosis with malformation of the feet (65) in a father and his son. Fontaine et al. (66) subsequently reported the same disorder in a three-generation family. A 30-year follow-up of one of the original patients and a further case were presented by Wilkie and Goodacre (67). Only one further case has been reported since (66, 68).

The patients presented with MFD and other signs, including ectrodactyly of the feet (6 of 7), syndactyly of the feet (6 of 7), ectrodactyly of the hands (1 of 7), syndactyly of the hands (1 of 7), retrognathia (6 of 7), malformed ears (6 of 7), cleft palate or bifid uvula (5 of 7), and ID (3 of 7) (68).

There is some overlap with patients who have split hand/split foot malformation type 1 (SHFM1), characterized by syndactyly, median clefts of hand and feet, and aplasia and/or hypoplasia of phalanges, metacarpals, and metatarsals. Additional findings in some SHMF1 patients were ID, ectodermal and craniofacial findings, and orofacial clefting. The SHMF1 patients have deletions in 7q21, and Birnbaum et al. (69, 70) identified tissue-specific enhancers in the DLX5/6 locus.

**AFD type Catania (OMIM 101805)**

This type of AFD was first reported by Opitz et al. (71) in a mother and her four sons from Catania, Sicilia. The mother was as severely affected as her sons making autosomal dominant inheritance more likely than X-linked inheritance, but mitochondrial inheritance is also possible as Wulfsberg et al. (72) described a second family 3 years later with an affected mother–daughter pair. The affected individuals have ID (all of 7) and microcephaly (5 of 6). The craniofacial features consist of downslanting palpebral fissures, a long philtrum, a short nose, malar hypoplasia, micrognathia, and low-set, posteriorly rotated ears. Limb anomalies were mild with brachyactyly (all of 7), syndactyly (5 of 6), clinodactyly of the fifth fingers (2 of 5), and hypoplasia of thumbs (5 of 6). Males also presented with hypospadias and cryptorchidism. The gene is still unknown.

**AFD type Richieri-Costa-Pereira (MIM 268305)**

In 1992, Richieri-Costa and Pereira described a new form of AFD (73) with short stature, Robin sequence, cleft mandible, pre- or post-axial hand anomalies and clubfoot. One year later, the same authors described another family (74) with similar anomalies. Several other authors reported similar patients with this condition. For a detailed review of this condition in 25 apparently unrelated Brazilian patients, see Ref. (75).

This condition most likely follows an autosomal recessive mode of inheritance; all but one patient, who is from France, originated from Brazil. Clinical evaluation of 28 patients revealed that microstomia, micrognathia, clubfeet and abnormal fusion of the mandible were present in all patients. Hypoplastic thumbs were noted in 96.2% of patients; 92.8% had minor ear anomalies; and 80% had absent lower incisors, which appears to be an important clinical sign to distinguish it from other MFDs. A total of 78.5% of patients presented with cleft palate/Robin sequence. Mesomelic shortening of upper and lower limbs was observed in 52% and 89%, respectively. Learning disabilities were also common (84%) (75).

Although the clinical phenotype appears to be very distinct, the causative gene is still unknown.

**AFD type Palagonia (MIM 601829)**

This type is characterized by oligodontia, frizzy hair, and short stature. The only article on this AFD was published by Sorge et al. (76). They described a Sicilian family with this most likely autosomal dominant condition. As females were more severely affected than males, X-linked dominant inheritance was also discussed. The patients presented with MFD are characterized by downslanting palpebral fissures, ectropion of the lower lids with absence of lower eyelashes, malar hypoplasia, and micrognathia. They have normal intelligence, oligodontia, short stature, frizzy hair, mild finger syndactyly, and vertebral anomalies, and had no further signs of an ectodermal dysplasia. The causative gene is still unknown.

In conclusion, a wide range of MFD and AFD phenotypes has been described over the years. During the last few years, the genetic bases of, e.g. Treacher Collins, Nager, and Miller syndromes as well as of AFD type Guion-Almeida, have been resolved. The genes responsible for these conditions are involved
in ubiquitous processes such as RNA transcription and splicing. Future studies are needed to understand why such processes lead to specific phenotypes and to discover the genetic bases of the remaining, still unresolved MFDs and AFDs.

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References


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