Elements of morphology: Standard terminology for the teeth and classifying genetic dental disorders

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Abstract
Dental anomalies occur frequently in a number of genetic disorders and act as major signs in diagnosing these disorders. We present definitions of the most common dental signs and propose a classification usable as a diagnostic tool by dentists, clinical geneticists, and other health care providers. The definitions are part of the series Elements of Morphology and have been established after careful discussions within an international group of experienced dentists and geneticists. The classification system was elaborated in the French collaborative network "TÊTECOU" and the affiliated
O-Rares reference/competence centers. The classification includes isolated and syndromic disorders with oral and dental anomalies, to which causative genes and main extroral signs and symptoms are added. A systematic literature analysis yielded 408 entities of which a causal gene has been identified in 79%. We classified dental disorders in eight groups: dental agenesis, supernumerary teeth, dental size and/or shape, enamel, dentin, dental eruption, periodontal and gingival, and tumor-like anomalies. We aim the classification to act as a shared reference for clinical and epidemiological studies. We welcome critical evaluations of the definitions and classification and will regularly update the classification for newly recognized conditions.

**KEYWORDS**
Anatomy and Histology, Classification, Craniofacial abnormalities, Rare diseases, Terminology, Tooth abnormalities

1 | **INTRODUCTION**

Tooth number, shape, size, structure, and/or position can be abnormal or altered. There may be delayed or absent tooth eruption. Alterations in periodontal, gingival tissue formation, and odontogenic tumors are also recorded. Teeth anomalies can occur isolated or form an integral part of syndromes. Incomplete penetrance and variability in expression may result in difficulties in diagnosing syndromes. The progress in our knowledge of causative genes and sequencing techniques has enabled diagnostic procedures using panels of genes all known to cause dental anomalies and recognize syndromic entities, which were initially identified as isolated (Prasad et al., 2016). Tooth development anomalies can be part of a large number of disorders, with variable genetic causes, in a variety of ways (Bloch-Zupan, Sedano, & Scully, 2012; Hall, 1994). Dental development is driven by a cascade of epithelial–mesenchymal interactions between oral ectoderm and cranial neural crest derived ectomesenchyme (Tucker & Sharpe, 2004). This process takes place from embryonic and fetal prenatal stages until adulthood, ending with the eruption and the completion of root development of the last third molar. Dental anomalies are morphologically diverse and appear at any time during dental development (Thesleff, 2014). Dental anomalies reflect specific disturbances of one or more stages of odontogenesis, roughly classified as tooth initiation, morphogenesis, cytodifferentiation, mineralization, and bone modeling occurring with eruption (Hennekam, Allanson, & Krantz, 2010).

No complete nosology of dental disorders is available, and only partial nosologies have been published describing specific pathologies such as amelogenesis imperfecta (Witkop Jr., 1988) or dentinogenesis imperfecta (de La Dure-Molla, Fournier, & Berdal, 2015). Here, we present our experience in the management of several thousand patients with dental manifestations as part of their rare disorders and offer an overview of established entities and their classification into isolated and syndromic dental disorders. The classification is only possible if defined terms are available to describe oral and dental findings. A standard terminology for lips, mouth, and oral region is available (Carey et al., 2009). Here, we provide a definition for each dental sign using the strategy of the Elements of Morphology series (Allanson, Biesecker, Carey, & Hennekam, 2009). In the classification, the primary diagnostic entry is the dental sign(s), followed by the main other medical manifestations. We added the causative gene(s) and protein and cross-reference with the international nomenclatures OMIM and Orphanet (Rath et al., 2012). We aim to facilitate offering a globally usable nomenclature of dental signs and symptoms and facilitate interactions between oral health specialists and other health care providers.

2 | **MATERIALS AND METHODS**

Rare Disease Reference Centers and affiliated Competence Centers of the French Rare Disorders Healthcare Network named “TÊTECOU” constitutes a multidisciplinary group of experts, working on diagnosis and management of individuals with rare disorders of the head and neck, including dental defects. The group of experts constituted a working group to defining dental anomalies and proposed a nosology of genetic dental disorders. The results have been endorsed by an international panel of experts taking into account all observations.

2.1 | **Defining dental anomalies**

Existing terminology of dental anomalies was analyzed by obtaining data from several databases, nomenclatures, and ontologies (Supplementary Data Table S1): HPO (Human Phenotype Ontology (Groza et al., 2015), Orphanet (Rath et al., 2012), NEN9313:2015, D[4]phenodent (Bloch-Zupan, 2004), ICD10-ICD11, and the standard terminology of Elements of Morphology for the lips, mouth, and oral region (Carey et al., 2009). When worded differently, the present definitions supersede the ones from Carey et al., 2009. Data collected were formatted according to Elements of Morphology series (Allanson et al., 2009).
| Group of dental anomaly/ name of disease | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|--------------------------|-------------|------------|---------|-------|-------------------|
| Dental agenesis (hypodontia/oligodontia/anodontia) |                      |            |            |         |       |                   |
| (1) Isolated                          |                      |            |            |         |       |                   |
| 1 Incisors, lower central, absence of | 147330                 | /           | /          | /       |       | Three old report, underdiagnosis case |
| 2 Teeth, congenital absence of with taurodontia ans sparse hair | 272980                 | 2731        | /          | /       |       |                   |
| 3 Tooth agenesis, selective, X-linked 1; STHAGX1 | 313500                 | XLD         | EDA        |         |       | Ectodysplasin A   |
| 4 Tooth agenesis, selective, 1, with or without orofacial cleft; STHAG1 | 106600                 | AD          | MSX1       |         |       | Homebox protein MSX-1 |
| 5 Tooth agenesis, selective, 2; STHAG2 | 602639                 | /           | AR         | 16q12.1 |       |                   |
| 6 Tooth agenesis, selective, 3; STHAG3 | 604625                 | 99798       | AD         | PAX9    |       | Paired box protein Pax-9 |
| 7 Tooth agenesis, selective, 4; STHAG4 | 150400                 | AD          | WNT10A     |         |       | Protein WNT-10A   |
| 8 Tooth agenesis, selective, 5; STHAG5 | 610926                 | 99798       | /          | 10q11.2-q21 |   |                   |
| 9 Tooth agenesis, selective, 7; STHAG7 | 616724                 | 99798       | AD         | LRP6    | Low-density lipoprotein receptor-related protein 6 |
| 10 Oligodontia-colorectal cancer syndrome | 608615                 | 300576      | AD         | AXIN2   |       | Axin-2            |
| 11 Ectodermal dysplasia 10A, hypohidrotic/hair/nail type, autosomal dominant | 129490                 | 238468181   | AD        | EDAR    |       | Ectodysplasin A receptor |
| 12 Ectodermal dysplasia 11A, hypohidrotic/hair/tooth type, autosomal dominant | 614940                 | AD/AR       | EDARADD   | EDAR-associated death domain |
| 13 Ectodermal dysplasia 11B, hypohidrotic/hair/tooth type, autosomal recessive | 614941                 | 238468, 248 | AD/AR     | EDARADD | EDAR-associated death domain |
| 14 Ectodermal dysplasia with natal teeth, Turnpenny type | 601345                 | 69083       | /          | /       |       | One family         |

(Continues)
### TABLE 1 (Continued)

| Group of dental anomaly/ name of disease | Phenotype | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|-----------|-------------------------|-------------|------------|---------|-------|---------------------|
| (2) Skin disorders                      |           |                         |             |            |         |       |                     |
| (2.1) Ectodermal dysplasia “classical”  |           |                         |             |            |         |       |                     |
| 15 Böök syndrome                        | 112300    | 1262                    | /           | /          | /       |       | Severe hyperhidrosis of the hands and feet, small hands, small nails |
| 16 Dermoodontodyplasia                   | 125640    | 1660                    | /           | /          | /       |       | Two families, probable underdiagnosis |
| 17 Ectodermal dysplasia 1, hypohidrotic, X-linked | 305100 | 238468, 181             | XLR         | EDA        |         |       | Abnormal development in two or more ectodermal structures (hair, nails, teeth, and sweat glands) without other systemic findings |
| 18 Ectodermal dysplasia 2, Clouston type | 129500    | 189                     | AD          | GJB6       | Gap junction protein beta 6 |
| 19 Ectodermal dysplasia 3, Witkop type  | 189500    | 2228                    | AD          | MSX1       | Homeobox protein MSX-1 |
| 20 Ectodermal dysplasia 8, hair/tooth/nail type | 602401 | 99672                   | AR          | 18q22.1-q22.3 |
| 21 Ectodermal dysplasia 10B, hypohidrotic/hair/tooth type, autosomal recessive | 224900 | 238468, 248             | AR          | EDAR      | Ectodysplasin A receptor |
| 22 Ectodermal dysplasia 11A, hypohidrotic/hair/tooth type, autosomal dominant | 614941 | 238468, 1810             | AR/AR       | EDARADD   | EDAR-associated death domain |
| 23 Ectodermal dysplasia 11B, hypohidrotic/hair/tooth type, autosomal recessive | 614941 | 238468, 248              | AR/AR       | EDARADD   | EDAR-associated death domain |
| 24 Ectodermal dysplasia/short stature syndrome | 616029 | 423454                   | AR          | GRHL2      | Grainyhead-like protein 2 homolog |
| 25 Ectodermal dysplasia                 | /         | /                       | AR          | KREMEN1    | KREMEN1 | Issa et al., 2016 |
| 26 Ectodermal dysplasia                 | /         | /                       | /           | GREM2      | GREMLIN-2 | Kantaputra et al., 2015 |
| 27 Ectodermal dysplasia                 | /         | /                       | /           | TSPPEAR    | TSPPEAR | Peled et al., 2016 |
| 28 Odontoonychodermal dysplasia         | 257980    | 2721                    | AD          | WNT10A     | Protein WNT-10A |
| 29 Schöpf-Schulz-Passarge syndrome      | 224750    | 90944                   | AR          | WNT10A     | Protein WNT-10A |
| 30 Trichodontal dysplasia               | 601453    | 3351                    | AD          | /          | /       | Four families, probable underdiagnosis |
|                                         |           |                         |             |            |         |       | Space scalp and slow growing hair |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| Wolf-Hirschhorn syndrome | 194190 | 280 | AD | MSX1, del4p15.1-15.2 | Hox protein MSX-1 | Growth and developmental delay, facial dysmorphology (Greek warrior helmet profile), intellectual disability |
| Cleft lip/palate-ectodermal dysplasia syndrome, CLPED1 | 225060 | 1991, 3253 | AR | NECTIN1(PVRL1) | Nectin cell adhesion molecule 1 | Cleft lip and palate, sparse scalp hair, malformed protruding ears, partial syndactyly of the fingers and toes, hypohidrotic ectodermal dysplasia |
| Cranioectodermal dysplasia 1 | 218330 | 1515 | AR | IFT122 | Intraflagellar transport protein 122 homolog | Other name: Sensenbrenner syndrome |
| Sagittal craniosynostosis, short stature, sparse scalp hair, small nails, short hand, short limbs, small anus, narrow thorax, joint laxity, chronic renal, and liver disease |
| Cranioectodermal dysplasia 2 | 613610 | 1515 | AR | WDR35 | WD repeat-containing protein 35 | |
| Cranioectodermal dysplasia 3 | 614099 | 1515 | AR | IFT43 | Intraflagellar transport protein 43 | |
| Cranioectodermal dysplasia 4 | 614378 | 1515 | AR | WDR19 | WD repeat-containing protein 19 | |
| EEC syndrome-1 | 129900 | 1896 | AD | 7q11.2-q21.3 | / | Anhidrotic ectodermal dysplasia, cleft lip, and palate |
| Orofacial cleft 8 | 129400 | 1991 | AD | TP63 | Tumor protein 63 | Anhidrotic ectodermal dysplasia, cleft lip, and palate |
| Rapp-Hodgkin syndrome | 129400 | 3022 | AD | TP63 | Tumor protein 63 | Anhidrotic ectodermal dysplasia, cleft lip, and palate |
| Ectodermal dysplasia, ectrodactyly, and macular dystrophy | 225280 | 1897 | AR | CDH3 | Cadherin 3 | Ectodermal dysplasia, split of hand and foot, syndactyly, macular dystrophy |
| Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 | 604292 | 1896 | AD | TP63 | Tumor protein 63 | Split of hands and feet, ectodermal dysplasia, deft lip/palate |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| Ectodermal dysplasia-syndactyly syndrome 1 | 613573 | 247820 | AR | NECTIN4(PVRL4) | Nectin cell adhesion molecule 4 | Ectodermal dysplasia, syndactyly |
| Hay-Wells syndrome | 106260 | 1071 | AD | TP63 | Tumor protein 63 | Syndactyly, scalp infections, ankyloblepharon, cleft lip/palate |
| Limb-mammary syndrome | 603543 | 69085 | AD | TP63 | Tumor protein 63 | Severe hand/foot anomalies and hypoplasia/aplasia of the mammary gland and nipple |
| Odontotrichoungual-digital-palmar syndrome | 601957 | 69082 | AD | / | / | One family | Space scalp hair, syndactyly, deep transverse palmar creases, small nails |
| Uncombable hair, retinal pigmentary dystrophy, dental anomalies, and brachydactyly | 191482 | 1264 | AD | / | / | One family | Space scalp hair, juvenile cataracts, retinal pigmentary dystrophy, short metacarpal |

(2.4) Skin disorders with neurologic disorder

| Incontinentia pigmenti | 308300 | 464 | XLD | IKBKG/NEMO | NF-kappa-B essential modulator | Abnormalities of the skin along Blaschko's lines, space scalp hair, small nails, central nervous system anomalies |
| Ectodermal dysplasia, hypohidrotic, with immune deficiency | 300291 | 98813 | XLD, AD | IKBKG/NEMO, NFKBIA | NF-kappa-B essential modulator | Hypohidrotic ectodermal dysplasia, immunodeficiency |

(2.5) Skin disorders with cardiopathy

| Cardiomyopathy, dilated, with woolly hair and keratoderma | 605676 | 65282 | AR | DSP | Desmoplakin | Cardiomyopathy with woolly hair, keratoderma |
| Dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis | 615821 | | AD | DSP | Desmoplakin |

(2.6) Skin disorders with skin blistering

| Ectodermal dysplasia/skin fragility syndrome | 604536 | 158668 | AR | PKP1 | Plakophilin 1 | Skin fragility as blistering, ectodermal dysplasia, dystrophis nails, space scalp hair, palmoplantar keratoderma |

(2.7) Others skin disorders syndrome

| Acral-renal-ectodermal-dysplasia lipodystrophic-diabetes (AREDYLD) | 207780 | 1133 | AR | / | / | Two families | Lipoatrophy, diabetes mellitus, facial dysmorphology, space scalp hair, renal disorder |
| Cerebellar ataxia and ectodermal dysplasia | 212835 | 1174 | / | / | / | Cerebellar ataxia and hypohidrotic ectodermal dysplasia |

(Continues)
| Group of dental anomaly/name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 55 Deafness, congenital, and onychodystrophy, autosomal dominant, DDOD | 124480 | 79499, 3231 | AD | ATP6V1B2 | Vacuolar V-ATPase protein | Congenital deafness, small nails, small terminal phalanges |
| 56 Ectodermal dysplasia, trichoedontoonychial type | 129510 | 1818 | / | / | / | Ectodermal dysplasia, focal linear dermal hypoplasia of the tip of the nose, bilateral amastia and athelia, mild nerve hearing loss |
| 57 Dermatoosteolysis, Kirghizian type | 221810 | 1657 | AR | / | / | One family | Recurrent skin ulceration, arthralgia, fever, fistulous osteolysis around joints, nail dystrophy, and keratitis with visual impairment or blindness |
| 58 Pilodental dysplasia with refractive errors | 262020 | 2892 | / | / | / | One family | Ectodermal dysplasia with normal sweating and fingernails, scalp hypotrichosis, pili annulati, follicular hyperkeratosis of trunk and limbs, marked hyperopia |
| 59 Progeroid short stature with pigmented nevi | 176690 | 2959 | AR | / | / | Premature aging, multiple pigmented nevi, lack of facial subcutaneous fat, microcephaly, short stature, sensorineural hearing loss, and intellectual disability |
| 60 Scalp-ear-nipple syndrome | 181270 | 2036 | AD | KCTD1 | BTB/POZ domain-containing protein KCTD1 | Aplasia cutis congenita of the scalp, breast, and ears anomalies (absent pinnae, bilateral amastia), cataract |
| 61 Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis | 614813 | 314394 | AR | POC1A | POC1 centriolar protein homolog A | Short stature, small nails, facial dysmorphology, space scalp hair, short hands, and feet |
| 62 Waardenburg syndrome, type 1 | 193500 | 894, 3440 | AD | PAX3 | Paired-box protein Pax-3 | Pigmentary abnormalities of the hair, skin, and eyes, congenital sensorineural hearing loss, wide nasal ridge |
| (3) Eye diseases |  |  | | | | |
| 63 Axenfeld-Rieger syndrome, type 1 | 180500 | 782 | AD | PITX2 | Pituitary homeobox 2 | Abnormal development of the anterior segment of the eye, failure of involution of periumbilical skin |
| Group of dental anomaly/names of disease | Phenotype | MIM number | Inheritance | Gene/locus | Protein | Notes |
|-----------------------------------------|-----------|------------|-------------|------------|---------|-------|
| Axenfeld-Rieger syndrome, type 2        | 601499    | AD         | 13q14       | FOXC1      | Forkhead box protein CI |
| Axenfeld-Rieger syndrome, type 3, Rieger or Axenfeld anomalies | 602482, 98978, 91483, 7922 | AD | FOXC1 | Forkhead box protein CI |
| Blepharocheilodontic syndrome, BCDS    | 119580    | AD         | 1997        | FOXC1      | Forkhead box protein CI |
| Congenital myopathy with excess of muscle spindles (Costello syndrome) | 218040 | AD | FOXC1 | Forkhead box protein CI |
| Dental anomalies and short stature | 601216 | AR | LTBP3 | Latent transforming growth factor beta binding protein 3 |
| Dental anomalies and short stature | 222500 | AR | SLCE2A42 | Solute transporter |
| Group of dental anomaly / name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| Dysostosclerosis                         | 224300               | 1782                    | AR          | SLC29A3    | Equilibrative nucleoside transporter 3 | Osteopetrosis, red-violet macular atrophy of skin, platyspondyly |
| Ellis-van Creveld syndrome               | 225500               | 289                     | AR          | EVC1, EVC2 | EvC ciliary complex subunit 1       | Chondrodysplasia (short limbs, short ribs, postaxial polydactyly), ectodermal dysplasia |
| Johanson-Blizzard syndrome              | 243800               | 2315                    | AR          | UBR1       | E3 ubiquitin-protein ligase UBR1     | Growth deficiency, intellectual disability, facial dysmorphology, pancreatic insufficiency |
| Kabuki syndrome                          | 147920               | 2322                    | AD          | KMT2D      | Histone-lysine N-methyltransferase 2D | Intellectual disability, postnatal dwarfism, facial dysmorphology, short fifth fingers, radiographic abnormalities of the vertebrae, hip joints, recurrent otitis |
| Kabuki syndrome 2                       | 300867               | /                       | XLD         | KDM6A      | Lysine-specific methyltransferase 6A |                                                                     |
| Rothmund-Thomson syndrome                | 268400               | 2909                    | AR          | RECQL4     | ATP-dependent DNA helicase Q4       | Skin atrophy, telangiectasia, hyper-and hypopigmentation, congenital skeletal abnormalities, short stature, premature aging, increased risk of malignant disease, space scalp hair, juvenile cataract |
| Sotos syndrome 1, SOTOS1                | 117550               | 821                     | AD          | NSD1, del19p13.2 | Histone-lysine N-methyltransferase H3 lysine-36 and H4 lysine-20 specific | Excessively rapid growth, acromegalic features, nonprogressive cerebral disorder with intellectual disability, facial dysmorphology |
| Weyers acrodental dysostosis             | 193330               | 952                     | AD          | EVC1, EVC2 | EvC ciliary complex subunit 1       | Enamel anomaly, Nail dystrophy, postaxial polydactyly, mild short stature |
| (5) Endocrine and gynecological diseases |                     |                         |             |            |                                    |                                                                     |
| Brachymetapody, anodontia, hypotrichosis, albinoidism | 211370               | 2713                    | /           | /          | /                                  | Short stature with particular shortening of the metacarpals and metatarsals, space scalp hair, albinoidism, multiple ocular abnormalities |
| Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1) | 308700               | 432, 478                | XL          | ANOS1 (KAL1) | Anosmin 1                          | Absent or incomplete sexual maturation, low levels of circulating gonadotropins and testosterone, abnormalities of the hypothalamic–pituitary axis |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|-------------------------------|-------------|------------|---------|-------|---------------------|
| 85 Hypogonadotropic hypogonadism 2 with or without anosmia | 147950 | AD | FGFR1 | Fibroblast growth factor receptor 1 |
| 86 Hypogonadotropic hypogonadism 3 with or without anosmia | 244200 | AD | PROKR2 | Prokineticin receptor 2 |
| 87 Hypogonadotropic hypogonadism 4 with or without anosmia | 610628 | AD | PROK2 | Prokineticin 2 |
| 88 Opitz GBBB syndrome, type II | 145410 | AD | SPECC1L | Cytoispin-A | Laryngotraheoesophageal cleft, cleft of lip and palate, genitourinary defects, intellectual disability, developmental delay |
| 89 Ulnar-mammary syndrome | 181450 | AD | TBX3 | T-box transcription factor TBX3 | Posterior limb deficiencies or duplications, apocrine/mammary gland hypoplasia and/or dysfunction, delayed puberty in males, genital anomalies |
| 90 Acrofacial dysostosis, Palaugia type | 601829 | XL | / | / | One family | Acrofacial dysostosis, short stature, facial dysmorphism |
| 91 Alagille syndrome | 118450 | AD | JAG1 | JAGGED-1 | Paucity of intrahepatic bile ducts, cholestasis, cardiac disease, skeletal abnormalities, ocular anomalies, facial dysmorphism |
| 92 Apert syndrome | 101200 | AD | FGFR2 | Fibroblast growth factor receptor 2 | Craniosynostosis, midface hypoplasia, syndactyly of the hands and feet with a tendency to fusion of bony structures |
| 93 Branchiooculofacial syndrome | 113620 | AD | TFFAP2A | Transcription factor AP-2-alpha | Branchial cleft sinus defects, ocular anomalies (microphthalmia, lacrimal duct obstruction), facial dysmorphism, conductive hearing loss |
| 94 Carpenter syndrome | 201000 | AR | RAB23 | Ras-related protein Rab-23 | Acrocephaly, variable synostosis, short fingers, syndactyly, congenital heart defects, growth retardation, intellectual disability, hypogenitalism, obesity |
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 95 Carpenter syndrome 2                 | 614976               |                         | AR          | MEGF8      | Multiple epidermal growth factor-like domains protein 8 | Multisuture craniosynostosis, polysyndactyly of the hands and feet, abnormal left-right patterning, obesity, umbilical hernia, cryptorchidism, congenital heart disease |
| 96 Char syndrome                        | 169100               | 46627                   | AD          | TFAP2B     | Transcription factor AP2 beta                          | Patent ductus arteriosus with facial dysmorphology, short fifth fingers |
| 97 Cleft palate with ankyloglossia      | 303400               | 324601                  | XL          | TBX22      | T-box transcription factor TBX22                      | Cleft palate with or without ankyloglossia |
| 98 Cleft palate deafness and oligodontia| 216300               | 2010                    | /           | /          | /                                                     | One family Cleft soft palate, bilateral conductive deafness, short halluces |
| 99 Holoprosencephaly 1                 | 236100               | 2162                    | IC, AD      | 21q22.3    | /                                                     | Malformation of the human forebrain |
| 100 Holoprosencephaly 2                | 157170               |                         | IC, AD      | SIX3       | Homeobox protein 5X3                                   | Lip and anterior cleft palate, hypotelorism, microcephaly, intellectual disability, scoliosis, chronic constipation |
| 101 Holoprosencephaly 3                | 142945               |                         | AD          | SHH        | Sonic hedgehog protein                                | |
| 102 Holoprosencephaly 4                | 142946               |                         | AD          | TGIF1      | Transforming growth factor beta induced factor 1       | |
| 103 Holoprosencephaly 5                | 609637               |                         | AD          | ZIC2       | Zinc finger protein ZIC 2                              | Alobar and semi-lobar holoprosencephaly |
| 104 Holoprosencephaly 7                | 610828               |                         | AD          | PTCH1      | Protein patched homolog 1                              | Semi-lobar holoprosencephaly |
| 105 Holoprosencephaly 9                | 610829               |                         | AD          | GLI2       | Zinc finger protein GLI2                               | Brain developmental defects, with or without overt forebrain cleavage abnormalities |
| 106 Orofaciodigital syndrome 1         | 311200               | 2750                    | XLD         | OFD1       | Oral-facial-digital syndrome 1 protein                 | Facial dysmorphology, fingers anomalies, alopecia |

(Continues)
| Group of dental anomaly/ name of disease | Phenylotype number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|--------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 107 Sener syndrome                      | 606156             | /                       | /           | /          | /       |       | Facial dysmorphism, thin hair, and dystrophic nails, mild developmental delay |
| 108 Single median maxillary central incisor | 147250             | 2162, 280200, 2286       | AD          | SHH        | Sonic Hedgehog protein | Severe to mild intellectual disability, congenital heart disease, cleft lip, and/or palate, facial dysmorphism, and less frequently hypopituitarism, hypotelorism, convergent strabismus, esophageal and duodenal atresia, cervical hemivertebrae, cervical dermoid, hypothyroidism, scoliosis, absent kidney, micropenis, and ambiguous genitalia |
| 109 Teebi-Shaltout syndrome              | 272950             | 3291                    | /           | /          | /       |       | Slow hair growth, scaphocephaly with prominent forehead, bitemporal depression, camptodactyly, caudal appendage with sacral dimple |
| 110 Treacher Collins syndrome 1         | 154500             | 861                     | AD, AR      | TCOF1, POLR1D, POLR1C | Treacle protein, RNA polymerase I subunit C, subunit D | Antimonogolid eyes, coloboma of the lid, micrognathia, microtia, cleft palate, hypoplastic zygomatic arches, macrostomia, ears anomaly/conductive hearing loss |
| 111 Van der Woude syndrome              | 119300             | 888                     | AD          | IRF6       | Interferon regulatory factor 6 | Pits and/or sinuses of the lower lip, and cleft lip and/or cleft palate |
| 112 Van der Woude syndrome 2            | 606713             | /                       | AD          | GRHL3      | Grainyhead-like protein 3 homolog | |
| 113 Williams-Beuren syndrome            | 194050             | 904                     | AD          | 7α11.23    | /       |       | Supravalvular aortic stenosis (SVAS), intellectual disability, pulmonary artery stenosis, distinctive facial features |
| (7) Cancers and tumors                  |                    |                         |             |            |         |       |                     |
| 114 Oligodontia-colorectal cancer syndrome | 114500             | 300576                  | AD          | AXIN2      | Axin-2  |       | Colorectal neoplasia |
| (8) Intellectual disabilities          |                    |                         |             |            |         |       |                     |
| 115 Down syndrome                      | 190685             | 870                     | Isolated cases | /          |         |       | Intellectual disability and facial dysmorphism, Risk of periodontal attachment loss |
| Group of dental anomaly/name of disease | Phenotype/MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|-------------------|
| 116 Glass syndrome                      | 612313               | 251019                  | AD          | SATB2      | DNA-binding protein SATB2 | Intellectual disability, facial dysmorphology, joint laxity, arachnodactyly |
| 117 Hypoparathyroidism-retardation-dysmorphism syndrome | 241410               | 2323                    | AR          | TBCE       | Tubulin specific chaperone E | Other name: Sanjad-Sakati syndrome |
| 118 Larger deletion of several genes on chromosome 17q21.31 | /                    | /                       | /           | /          | /      | Tan et al., 2009, see also Koolen-De Vries syndrome (MIM 610443) |
| 119 Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism | 607694               | 77295, 447893, 137639, 447896 | AR          | POLR3A     | DNA-directed RNA polymerase III subunit RPC1 | Neurodegenerative disorder, progressive motor decline, (spasticity, ataxia, tremor), cerebellar signs, mild cognitive regression |
| 120 Leukodystrophy, hypomyelinating, 8, with or without oligodontia and/or hypogonadotropic hypogonadism | 614381               | 88637                   | AR          | POLR3B     | DNA-directed RNA polymerase III subunit RPC2 | Cerebellar ataxia and mild intellectual disabilities associated with diffuse hypomyelination apparent on brain MRI |
| 121 Tetramalic deficiencies, ectodermal dysplasia, deformed ears, and others anomalies | 273400               | 2723                    | /           | /          | /      | Malformations of all four extremities, small nails, ear anomalies, space scalp hair, hyperhidrosis, nasolacymal duct obstruction |

**Supernumerary teeth**

| (1) Isolated |
|--------------|
| 122 Teeth, supernumerary | 187100 | / | / | / | / | Two families, probable underdiagnosis |

| (2) Eye diseases |
|------------------|
| 124 Nance-Horan syndrome | 302350 | 627 | XLD | NHS | Nance-Horan syndrome protein | With screwdriver shape incisor, and molar cusp anomaly |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|----------------------|-------------------------|-------------|-----------|---------|-------|---------------------|
| 125 Opitz GBBB syndrome, type I         | 300000               | 2745, 306597            | WLR         | MID1      | E3 ubiquitin-protein ligase Midline-1 | Hypertelorism, hypoplasia, cleft lip/palate, laryngotracheoesophageal abnormalities, imperforate anus, developmental delay, cardiac defects |
| (3) Bone diseases                       |                      |                         |             |           |         |       |                     |
| 126 Brachydactyly, type B1              | 113000               | 93383                   | AD          | ROR2      | Tyrosine-protein kinase transmembrane receptor ROR2 | Severe malformations of the hands and feet (short fingers, absence of nails) |
| 127 Cleidocranial dysplasia             | 119600               | 1452                    | AD          | RUNX2     | RUNT-related transcription factor 2 | Open skull sutures with bulging calvaria, hypoplasia or aplasia of the clavicles, wide pubic symphysis, short middle phalanx of the fifth fingers, vertebral malformation |
| Cleidocranial dysplasia, forme fruste, dental anomalies only | 119600               | AD                      | RUNX2       | RUNT-related transcription factor 2 |
| Cleidocranial dysplasia, forme fruste, with brachydactyly | 119600               | AD                      | RUNX2       | RUNT-related transcription factor 2 |
| 128 Craniosynostosis and dental anomalies | 614188               | 284149                  | AR          | IL11RA    | Interleukine 11 receptor antagonist | Craniosynostosis, maxillary hypoplasia, syndactyly, clinodactyly |
| 129 Odontomas dysphagia syndrome        | 164330               | 2724                    | /           | /         | One family | Hypertrophy of the smooth muscles of the esophagus, severe dysphagia |
| 130 Robinow syndrome, autosomal recessive | 268310               | 97360, 1507             | AR          | ROR2      | Tyrosine-protein kinase transmembrane receptor ROR2 | Facial dysmorphology (frontal bossing, hypertelorism, and broad nose), short-limbed dwarfism, vertebral segmentation, short stature, clinodactyly, short hand, genital hypoplasia |
| 131 Robinow syndrome, autosomal dominant 1 | 180700               | 97360, 3107             | AD          | WNT5A     | Protein Wnt-5a | |
| 132 Robinow syndrome, autosomal dominant 3 | 616894               | 97360, 3107             | AD          | DVL3      | Segment polarity protein disheveled homolog | |
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|----------------------|--------------------------|-------------|------------|---------|-------|---------------------|
| **133** Trichorhinophalangeal syndrome, type I | 190350 | 77258 | AD | TRPS1 | Zing finger transcription factor TRPS1 | Sparse scalp hair, broad nasal tip, long flat philtrum, thin upper vermilion border, protruding ears, skeletal abnormalities (cone-shaped epiphyses at the phalanges, hip malformations), short stature |
| **134** Trichorhinophalangeal syndrome, type III | 190351 | AD | TRPS1 | Zing finger transcription factor TRPS1 | Space scalp hair, convex nasal ridge, long upper lip, short metacarpal phalanges |
| **135** Gardner syndrome | 175100 | 733, 220460, 247806, 79665, 99818 | AD | APC | Adenomatous polyposis coli protein | Adenomatous polyps of the colon and rectum, predisposition to cancer |
| **136** Natal teeth-intestinal pseudointestinum-patent ductus syndrome | 243185 | 1654 | / | / | / | One family | Patent ductus arteriosus, intestinal pseudoobstruction evident from birth |
| **137** Steatocystoma multiplex-natal teeth syndrome | 184510 | 3184 | / | / | / | One family | Multiple steatocystomas |
| **138** Beare-Stevenson cutis gyrata syndrome | 123790 | 1555 | AD | FGFR2 | Fibroblast growth factor receptor 2 | Craniosynostosis, ear defects, cutis gyrata, acanthosis nigricans, anogenital anomalies, skin tags, prominent umbilical stump |
| **139** Mohr syndrome | 252100 | 2751 | / | / | / | Poly-, syn-, and brachydactyly, lobate tongue with papilliform protuberances, angular form of the alveolar process of the mandible, supernumerary sutures in the skull, an episodic neuromuscular disturbance |

**Dental morphology anomalies (size and shape)**

(1) **Microdontia**

(1.1) **Isolated**

| Dental anomaly | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------|----------------------|--------------------------|-------------|------------|---------|-------|---------------------|
| **140** Dentin dysplasia, type I, with microdontia and misshapen teeth | 125400 | 314721, 1653 | AR | SMOC2 | Secreted modular calcium binding protein 2 | One family |
| **141** Taurodontism, microdontia, and dens invaginatus | 313490 | / | / | / | One family | |

(1.2) **Syndromic**

(Continues)
| Group of dental anomaly/name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|-------------------------|-------------|-----------|---------|-------|---------------------|
| Cartilage-hair hypoplasia              | 250250               | 175                     | AR          | RMRP      | Mitochondrial RNA-processing endoribonuclease | Short-limbed dwarfism, slow growing hair, short stature, short hand, metaphyseal lesions |
| Craniofacial dysmorphism, skeletal anomalies, and intellectual disability syndrome | 213980               | 1394                    | AR          | TMCO1     | Calcium load-activated calcium channel | Facial dysmorphology, multiple malformations of the vertebrae and ribs, and intellectual disability |
| Deafness, congenital with inner ear agenesis, microtia, and microdactyly | 610706               | 90024                   | AR          | FGF3      | Fibroblast growth factor 3 | Congenital deafness with inner ear agenesis, microtia |
| Filippi syndrome                       | 272440               | 3255                    | AR          | CKAP2L    | Cytoskeleton associated protein 2 like | Short stature, microcephaly, syndactyly, intellectual disability, and facial dysmorphology |
| Genitopatellar syndrome                | 606170               | 85201                   | AD          | KAT6B     | Histone acetyltransferase KAT6B | Fusion of the proximal or distal interphalangeal joints (arthrogryposis of hips and knees), patellar aplasia |
| Gorlin-Chaudhry-Moos syndrome, GCMS    | 233500               | 2095                    | /           | /         | /       | Stocky body build, hypertrichosis, craniosynostosis, conductive hearing loss, normal intelligence, hyperopia, facial dysmorphology, hypoplastic distal phalanges, umbilical hernia, and genital hypoplasia |
| Lenz-Majewski hyperostotic dwarfism   | 151050               | 2658                    | AD          | PTDS5I    | Phosphatidylserine synthase 1 | Intellectual disability, facial dysmorphology, loose/atrophic skin, distal limb anomalies, short hand, hyperostotic dwarfism |
| Ohdo syndrome                          | 249620               | 2728                    | /           | /         | /       | Intellectual disability, congenital heart disease, blepharophimosis, blepharoptosis, hearing impairment |
| Microcephalic osteodysplastic primordial dwarfism, type II (MOPD II) | 210720               | 2637                    | AR          | PCNT      | Pericentrin | Intrauterine growth retardation, severe proportionate short stature, and microcephalic dwarfism |
| Microcephaly, macrotia, and intellectual disability | 602555               | /                       | /           | /         | One family | Microcephaly, intellectual disability, huge ears with very large lobules, median frenulum of the upper lip, ptosis, bilateral ureterohydronephrosis secondary to vesicoureteral reflux |
| Table 1 (Continued) |
|---------------------|
| **Group of dental anomaly/ name of disease** | **Orphanet number (ORPHA)** | **MIM number** | **Inheritance** | **Gene/locus** | **Protein** | **Notes** | **Main manifestations** |
| 152 Multiple congenital anomalies-hypotonia-seizures syndrome 2 | 300496 | 300868 | XLR | PIGA | Phosphatidylinositol N-acetylglucosaminyl transferase subunit A | Facial dysmorphology, neonatal hypotonia, myoclonic seizures, and variable congenital anomalies involving the central nervous, cardiac, urinary systems |
| 153 Rosselli-Gulienetti syndrome | / | 225000 | / | / | / | One family | Anhidrosis, hypotrichosis, small nails, cleft lip and palate, deformity of the fingers and toes, malformation in the genitourinary system |
| 154 Seckel syndrome 1 | 808 | 210600 | AR | ATR | Serine/threonine-protein kinase ATR | Intrauterine growth retardation, dwarfism, microcephaly with intellectual disability, facial dysmorphism |
| 155 Smith-Lemli-Opitz syndrome | 818 | 270400 | AR | DHCR7 | 7-dehydrocholesterol reductase | Multiple congenital malformation (cardiovascular, genitointestinal), intellectual disability, autistic traits, growth retardation |
| 156 Symphalangism, distal, with microdontia, dental pulp stones, and narrowed zygomatic arch | / | 606895 | / | / | / | One family | Fusion of the proximal or distal interphalangeal joints |
| 157 Turner syndrome (2) Macrodontia | / | / | / | / | / | Short stature, ovarian failure |
| 158 KBG syndrome | 2332 | 148050 | AD | ANKRD11 | Ankyrin repeat domain containing protein 11 | Macrodontia of the upper central incisors, facial dysmorphism, short stature, skeletal anomalies, and neurologic involvement that includes global developmental delay, seizures, and intellectual disability |
| 159 Microphthalmia, syndromic 2 | 568, 2712 | 300166 | XLD | BCOR | BCL6 corepressor | Congenital cataract, microphthalmia, atrial septal defect |
| 160 Otodental dysplasia chromosome deletion syndrome | 166750 | 99806, 2791 | AD | FGF3, FADD | Fibroblast growth factor 3, FAS-associated death domain protein | Sensorineural hearing loss, ocular coloboma, facial dysmorphology |
| 161 Surnumerary X Klinefelter syndrome | 484 | / | / | / | / | With taurodontism | Hypogonadism, intellectual disability, genital anomalies |
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|---------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| (3) Talon cusp                          |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 162                 | 180849                  | AD          | CREBBP, EP300 | CREB binding protein; P300 | Intellectual disability, postnatal growth deficiency, microcephaly, short and broad thumbs and halluces, facial dysmorphism |
| Talon cusp                              |                     | 783, 353277             |             |            |         |       |                     |
| Talon cusp                              |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 163                 | 605282                  | AR          | CHSY1      | Chondroitin sulfate synthase 1 | One patient with hypodontia |
| Talon cusp                              | 363417              |                         |             |            |         |       | Intellectual disability, sensorineural deafness, growth retardation, broad fingers |
| Talon cusp                              | 363417              |                         |             |            |         |       |                     |
| Talon cusp                              |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 164                 | 200970                  | /           | /          | /       | One family | Juvenile glaucoma |
| Talon cusp                              | 2561                |                         |             |            |         |       |                     |
| Talon cusp                              |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 165                 | 206900                  | AD          | SOX2       | Transcription factor SOX-2 | Microphthalmia (with or without defects of the optic nerve, optic chiasm, and optic tract), brain anomalies, seizures, motor disability, neurocognitive delays, sensorineural hearing loss, esophageal atresia |
| Talon cusp                              | 77298               |                         |             |            |         |       |                     |
| Talon cusp                              |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 166                 | 200110                  | AD          | TWIST2     | Twist-related protein 2 | Ectodermal dysplasia, ablepharon, macrostomia, microtia, redundant skin, sparse scalp hair, variable abnormalities of the nipples, genitalia, syndactyly of hands and feet, normal intellectual and motor development, growth retardation |
| Talon cusp                              | 920                 |                         |             |            |         |       |                     |
| Talon cusp                              |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 167                 | 242900                  | AR          | SMARCAL1   | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1 | Bulbous dental crown, thin and short root |
| Talon cusp                              | 1830                |                         |             |            |         |       | Combined immunodeficiency with associated or syndromic features: Spondyloepiphyseal dysplasia with a peculiar clinical phenotype, short stature, facial dysmorphism, numerous lentigines, a slowly progressive immune defect, and an immune-complex nephritis which leads to death at about age 8 years |
| Talon cusp                              |                     |                         |             |            |         |       |                     |
| Talon cusp                              | 168                 | /                      | AR          | TCTEX1D2   | TCTEX1D2 protein | Congenital heart defects, laterality defects |
| Talon cusp                              | /                   |                         |             |            |         |       |                     |
| Talon cusp                              |                     |                         |             |            |         |       |                     |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|----------------------|--------------------------|-------------|-----------|---------|-------|----------------------|
| Enamel anomalies (affecting temporary and permanent teeth) | | | | | | | |
| (1) Isolated | | | | | | | |
| 169 Amelogenesis imperfecta, type IA | 104530 | 88661, 100031 | AD | LAMB3 | Laminin beta 3 | | |
| 170 Amelogenesis imperfecta, type IB | 104500 | | AD | ENAM | Enamelin | | |
| 171 Amelogenesis imperfecta, type IC | 204650 | | AR | ENAM | Enamelin | | |
| 172 Amelogenesis imperfecta, type IF | 616270 | | AR | AMBN | Ameloblastin | | |
| 173 Amelogenesis imperfecta, type IH | 616221 | 88661, 100031, 100032 | AR | ITGB6 | Integrin beta 6 | | |
| 174 Amelogenesis imperfecta, hypoplastic/hypomaturation type 1E | 301200 | 88661, 100033 | XLD | AMELX | Amelogenin | | |
| 175 Amelogenesis imperfecta, hypoplastic/hypomaturation, X-linked 2 | 301201 | 88661, 100031 | XL | / | / | | |
| 176 Amelogenesis imperfecta, type IIA1 | 204700 | 88661, 100033 | AR | KLK4 | Kallikrein-related peptidase 4 | | |
| 177 Amelogenesis imperfecta, type IIA2 | 615259 | | AR | MMP20 | Matrix metalloproteinase 20 | | |
| 178 Amelogenesis imperfecta, hypomaturation type, IIA3 | 613211 | | AR | WDR72 | WD repeat-containing protein 72 | | |
| 179 AIH, hypomature type, IIA4 | 614832 | | AR | C4orf26 | Uncharacterized protein C4orf26 | | |
| 180 Amelogenesis imperfecta, type IIA5 | 615587 | | AR | SLC24A4 | Sodium/potassium/calcium exchanger 4 | | |
| 181 Amelogenesis imperfecta, type III | 130900 | 88661, 100032 | AD | FAM83H | Protein FAM83H | | |
| 182 Amelogenesis imperfecta, type IV | 104510 | 88661, 100034 | AD | DLX3 | Homeobox protein DLX-3 | With taurodontism | |
| 183 Amelogenesis imperfecta | / | / | / | ARHGAP6 | Rho GTPase-activating protein 6 | | |
| 184 Amelogenesis imperfecta | / | / | AD | LAMA3 | Laminin alpha 3 | Kim et al., 2013 | |
| 185 Amelogenesis imperfecta | / | / | AD | AMTN | Amelotin | Smith et al., 2016 | |
| 186 Amelogenesis imperfecta | / | / | AR | ACPT | Acid phosphatase testicular | Seymen et al., 2016 | |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number (ORPHA) | Orphanet number | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|-------------------------------|-----------------|-------------|------------|---------|-------|---------------------|
| Amelogenesis imperfecta                 | 187                           | /               | AR          | GPR68      | Proton sequencing G protein-coupled receptor | Parry et al., 2016 |
| Epithelial recurrent erosion dystrophy  | 188                           | 122400          | AD          | COL17A1    | Collagen 17 alpha 1                         |                     |
| Amelogenesis imperfecta                 | 189                           | /               | AR          | RELT       | Tumor necrosis factor receptor superfamily | Kim et al., 2018    |

(2) Skin disorders

| Amelogenesis imperfecta                 | 190                           | 104570          | /           | /          | /      | /     | Onycholyis with subungual hyperkeratosis, hypohidrosis |
| Arthrogryposis and ectodermal dysplasia | 191                           | 601701          | /           | /          | /      | /     | Trichodyplasia, dry skin with scaling, hyperchromic spots on the limbs, hyperkeratosis, small nails, short of stature, kyphoscoliosis, facial dysmorphism, ocular anomalies |
| Cutaneous telangiectasia and cancer syndrome, familial | 192                           | 614564          | AD          | ATR        | Serine/threonine-protein kinase ATR         | Cutaneous telangiectasia, mild developmental anomalies of hair and nails, predisposition to cancer (predominantly oropharyngeal) |
| Ectodermal dysplasia-syndactyly syndrome 2 | 193                           | 613576          | AR          | 7p21.2-p14.3 | /      | /     | One family, probable undiagnosis |
| Ectodermal dysplasia, hypohidrotic, with hypothyroidism and agenesis of the corpus callosum | 194                           | 225040          | /           | /          | /      | /     | Probable contiguous to MIM 225050, Severe intellectual disability, hypohidrotic ectodermal dysplasia, primary hypothyroidism, agenesis of the corpus callosum |
| Epidermolysis bullosa, generalized atrophic benign | 195                           | 226650          | AR          | LAMA3      | Laminin alpha 3                            | Blistering of the skin |
| Epidermolysis bullosa, junctional, Herlitz type | 196                           | 226700          | AR          | LAMA3      | Laminin alpha 3                            |                     |
| Epidermolysis bullosa, junctional, Herlitz type | 197                           | 226700          | AR          | LAMB3      | Laminin beta 3                             |                     |
| Epidermolysis bullosa, junctional, non-Herlitz type | 198                           | 226650          | AR          | LAMB3      | Laminin beta 3                             |                     |
| Group of dental anomaly/name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 199 Epidermolysis bullosa, junctional, Herlitz type | 226700 | 79404 | AR | LAMC2 | Laminin gamma 2 |
| 200 Epidermolysis bullosa, junctional, non-Herlitz type | 226650 | 79402, 79405, 251393, 89840 | AR | LAMC2 | Laminin gamma 2 |
| 201 Epidermolysis bullosa, junctional, non-Herlitz type | 226650 | AR | ITGB4 | Integrin beta 4 |
| 202 Epidermolysis bullosa of hands and feet | 131800 | 79400 | AD | ITGB4 | Integrin beta 4 |
| 203 Epidermolysis bullosa, junctional with pyloric atresia | 226730 | 79403 | AR | ITGB4 | Integrin beta 4 |
| 204 Epidermolysis bullosa, junctional with pyloric atresia | 226730 | AR | ITGA6 | Integrin alpha 6 |
| 205 Epidermolysis bullosa, junctional, localisata variant Epidermolysis bullosa, junctional, non-Herlitz type | 226650 | 79402, 79405, 251393, 89840 | AR | COL17A1 | Collagen 17 alpha 1 |
| 206 Epidermolysis bullosa, late-onset localized junctional with intellectual disability | 226440 | 231556 | / | / | / | Late-onset epidermolysis bullosa localized to the anterior aspect of the legs, small nails, intellectual disability |
| 207 Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis | 607626 | 59303 | AR | CLDN1 | Claudin 1 | Space scalp hair, scarring alopecia, sclerosing cholangitis, leukocyte vacuolization, hepatic disease |
| 208 IFAP syndrome with or without BRESHECK syndrome | 308205 | 85284, 2273 | XLR | MBTPS2 | Membrane-bound transcription factor site-2 protease | Ichthyosis follicularis, alepecia, photophobia |
| 209 Immunodeficiency 9 | 612782 | 169090, 317428 | AR | ORAI1 | Calcium release-activated calcium channel protein 1 | Combined Immunodeficiency with associated or syndromic features: recurrent infections, myopathy, autoimmunity, ectodermal dysplasia |
| 210 Keratosis follicularis spinulosa decalvans, autosomal dominant; KFSD | 612843 | 2340 | / | / | / | Follicular hyperkeratosis, progressive cicatricial alopecia, photophobia, corneal dystrophy, facial erythema |
| Group of dental anomaly/name of disease | Phenotype/MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|---------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 211 Laryngoonychocutaneous syndrome     | 245660              | 2607                    | AR          | LAMA3      | Laminin alpha 3 | Hoarseness, dystrophic changes in the nails, and chronic bleeding, crusted lesions of the skin of the face, respiratory obstruction |
| 212 LADD syndrome                      | 149730              | 2363                    | AD          | FGFR3      | Fibroblast growth factor receptor 3 | Anomalies of lacrimal glands and ducts, salivary glands and ducts, ears, distal limb segments, hearing loss, fingers malformation |
| 213 LADD syndrome                      | 149730              | AD                      | FGFR10      |            |         |       |                     |
| 214 LADD syndrome                      | 149730              | AD                      | FGFR2       |            |         |       |                     |
| 215 Naegeli-Franceschetti-Jadassohn syndrome | 161000              | 69087                   | AD          | KRT14      | Keratin 14 | Reticular cutaneous pigmentation, hypohidrosis, moderate hyperkeratosis of the palms and soles, absence of fingerprints |
| 216 Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic | 163200              | 2612                    | /           | NRAS       | GTPase NRas | Sebaceous nodule (often on the face), variable ipsilateral abnormalities of the central nervous system, ocular anomalies, skeletal defects |
| 217 Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic | 163200              | Isolated cases          | HRAS        | GTPase HRas |         |       |                     |
| 218 Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic | 163200              | Isolated cases          | KRAS        | GTPase KRas |         |       |                     |
| 219 Shaheen syndrome                   | 615328              | 363523                  | AR          | COG6       | Conserved oligomeric Golgi complex subunit 6 | Severe intellectual disability, hypohidrosis, hyperkeratosis of the palms and soles, mild microcephaly |
| 220 Trichoedontoonychial dysplasia with bone deficiency | 275450              | 3355                    | /           | /          | /       | One family | Ectodermal dysplasia, supernumerary nipples, nevus pigmentosus, bone deficiency in the frontoparietal region |
| 221 Tuberous sclerosis-1               | 191100              | 805                     | AD          | TSC1       | Hamartin | Hamartomas in multiple organ systems (brain, skin, heart, kidneys, lung) |
| 222 Tuberous sclerosis-2               | 613254              | AD                      | TSC2        | Tuberin     |         |       |                     |

(Continues)
| Group of dental anomaly/ name of disease | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| **(3) Eye diseases**                   |                         |             |            |         |       |                     |
| 223 Jalili syndrome                    | 217080                  | 1873        | AR         | CNNM4   | Metal transporter CNNM4 | Cone-rod dystrophy of the retina |
| 224 Microphthalmia with linear skin defects | 309801 | 2556 | XLD | Xp.22 | Microphthalmia and linear skin defects |
| 225 Microphthalmia, dermal aplasia, and sclerocornea | 309801 | 2556 | XLD | Xp.22 | Microphthalmia and linear skin defects |
| 226 Microphthalmia, syndromic 1, MCOPS1 | 309800 | 568 | XL | NAA10 | N-Alpha-acetyltransferase 10 | Microphthalmia or anophthalmia, defects in the skeletal and genitourinary systems, ear, digits anomalies |
| **(4) Bone diseases**                  |                         |             |            |         |       |                     |
| 227 Alopecie-contracturs dwarfis intellectual disability syndroms | 203550 | 1005 | / | / | / | Short stature, kyphoscoliosis, bilateral dislocation of the hips, contracture of multiple joints present from birth, facial dysmorphology, ichthyosis, ectrodactyly, intellectual disability, photosphobia |
| 228 Cockayne syndrome, type A          | 216400                  | 191, 90321, 90322, 90324 | AR | ERCC8 | DNA excision repair protein ERCC-8 | Slow growth and development, cachectic dwarfism, cutaneous photosensitivity, thin, dry hair, a progeroid appearance, progressive pigmenatary retinopathy, sensorineural hearing loss |
| 229 Focal dermal hypoplasia            | 305600                  | 2092        | XLD        | PORCN   | Porcupine | Atrophy and linear pigmentation of the skin, hemiation of fat through the dermal defects, multiple papillomas of the mucous membranes or skin, digits anomaly, ocular anomaly, intellectual disability |
| 230 Hallermann-Streiff syndrome, HSS   | 234100                  | 2108        | /          | /      | / | Natal teeth |
| 231 Hamamy syndrome                    | 611174                  | 314555      | AR         | IRX5    | Iroquois homebox 5 | Hypertelorism with midface prominence, myopia, intellectual disability, bone fragility |
| 232 Kenny-Caffey syndrome, type 1      | 244460                  | 93324, 2333 | AR | TBCE | Tubulin specific chaperone E | See also Sanjad Sakati syndrome | Seizure anomaly, cortical thickening, medullary stenosis |
| Group of dental anomaly/name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 233 McCune-Albright syndrome            | 174800               | 562                     | /           | GNAS1      | Protein ALEX |       | Bone skeleton, skin, and endocrine system anomalies |
| 234 Mesomelia synostosis syndrome       | 600383               | 2496                    | Isolated cases | 8q13 del   | /       |       | Acral synostoses combined with ptosis, hypertelorism, palatal abnormality, congenital heart disease, and ureteral anomalies |
| 235 Metaphyseal dysplasia with maxillary hypoplasia with or without brachydactyly | 156510               | 2504                    | AD          | RUNX2      | Runt-related transcription factor 2 |       | Bone anomalies (metaphyseal flaring of long bones), enlargement of the medial halves of the clavicles, maxillary hypoplasia, short hand, short stature, facial dysmorphology |
| 236 Mucopolysaccharidosis Ih             | 607014               | 579                     | AR          | IDUA       | Alpha-L-iduronidase |       | Coarse facies, corneal clouding, intellectual disability, hemias, dysostosis multiplex, hepatosplenomegaly, axial hypotonia |
| 237 Mucopolysaccharidosis IVA (Morquio A) | 253000               | 582, 309297             | AR          | GALNS      | N-Acetylgalactosamine-6-sulfatase |       | Short stature, skeletal dysplasia, dental anomalies, corneal clouding |
| 238 Multiple joint dislocations, short stature, craniofacial dysmorphism, with or without congenital heart defects | 245600               | 284139                  | AR          | B3GAT3     | Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3 |       | Multiple joint dislocations, short stature, craniofacial dysmorphism with or without congenital heart defects |
| 239 Oculodentodigital dysplasia, ODDDD   | 164200               | 2710                    | AD          | GJA1       | Connexin 43 |       | Wide nasal bridge with underdeveloped ala nasi, broad columella, prominent epicanthus, microphalonia, microcornea, syndactyly, clinodactyly |
| 240 Oculodentodigital dysplasia, autosomal recessive | 257850               | 2710                    | AR          | GJA1       | Connexin 43 |       | Diminished fetal activity, obesity, muscular hypotonia, intellectual disability, short stature, hypogonadotropic hypogonadism, small hands and feet |
| 241 Prader-Willi syndrome                | 178270               | 739                     | Isolated cases | SNRPN      | Small nuclear ribonucleoprotein-associated protein N |       | (Continues) |
| Group of dental anomaly/ name of disease | Orphanet number (ORPHA) | Phenotype MIM number | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|-------------------------|---------------------|-------------|------------|---------|-------|---------------------|
| Prader-Willi syndrome                    | 176270                  | Isolated cases      | NDN         | Necdin     | RAC-alpha serine/threonine-protein kinase | With gingival overgrowth | Asymmetric and disproportionate overgrowth of body parts, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, vascular malformations |
| Proteus syndrome, somatic                | 176920                  | Sporadic mosaic     | AKTI        | RAC-alpha serine/threonine-protein kinase |          |       |                    |
| Pseudohypoparathyroidism Ia              | 103580                  | AD                  | GNAS        | Protein ALEX |          |       | Short stature, obesity, ocular disorder, osteoporosis, hypercalcemia, hyperphosphatemia, elevated PTH, short fingers, intellectual disability |
| Pycnodysostosis                          | 265800                  | AR                  | CTSK        | Cathepsine K |          |       | Deformity of the skull, acroosteolysis, osteosclerosis, fragility of bone |
| Raine syndrome                           | 259775                  | AR                  | FAM20C      | Cathepsine K |          |       | Neonatal osteosclerotic bone dysplasia, usually death within the first few weeks of life |
| Rickets, vitamin D-resistant, type RA    | 277440                  | AR                  | VDR         | Vitamin D receptor |          |       | Hypocalcemia, secondary hyperparathyroidism, osteomalacia, and osteitis fibrosa cystica, normal serum 25-hydroxyvitamin D, markedly increased serum 1,25-dihydroxyvitamin D |
| Trichodontoosseous syndrome               | 190320                  | AD                  | DLX3        | Distal less homeobox 3 | With taurodontism | Strikingly curly hair, mild increase in bone density |
| Skeletal dysplasia with multiple dislocations | /                      | AD                  | SLC10A7     | SLC10A7 |          |       | Short stature, joints dislocations, craniofacial dysmorphism |
| XFE progeroid syndrome, XFEPS             | 610965                  | AR                  | ERCC4       | DNA repair endonuclease XPF |          |       | Dwarfism, cachexia, and microcephaly |
| Autoimmune polyendocrinopathy syndrome, type I (APECED) | 240300                  | AR, AD              | AIRE        | Autoimmune regulator |          |       | The presence of two of three major clinical symptoms: Addison disease and/or hypoparathyroidism and/or chronic mucocutaneous candidiasis-disease of immune dysregulation: chronic mucocutaneous candidiasis, polyendocrinopathy |
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| (6) Renal diseases                     |                      |                         |             |            |         |       |                     |
| 252 Arthrogryposis, renal dysfunction, and cholestasis 1 | 208085 | 2697 | AR | VPS33B, VIPAR | Vacular protein sorting-associated protein 33B, VPS33B interacting protein | Multiplex congenita with jaundice and renal dysfunction |
| 253 Enamel renal syndrome, amelogenesis imperfecta, type IG | 204690 | 1031, 171836 | AR | FAM20A | Pseudokinase FAM20A | Nephrocalcinosis |
| 254 Hypomagnesemia 5, renal, with ocular involvement | 248190 | 2196 | AR | CLDN19 | Claudin-19 | Renal magnesium wasting with hypercalcinosis, progressive renal failure, ocular anomaly |
| 255 Hypomagnesemia 3, renal | 248250 | 31043 | AR | CLDN16 | Claudin-16 | Hypomagnesemia with hypercalciuria and nephrocalcinosis, progressive renal disorder characterized by excessive urinary Ca(2+) and Mg (2+) excretion |
| 256 Pseudohypoaldosteronism, type RA | 145260 | 757, 88938 | AD | 1q31-q42 | / | Hyperkalemia despite normal renal glomerular filtration, hypertension |
| 257 Renal cysts and diabetes syndrome | 137920 | 93111 | AD | HNF1B | Hepatocyte nuclear factor 1-beta | Renal cysts and diabetes |
| (7) Intellectual disabilities         |                      |                         |             |            |         |       |                     |
| 258 Chromosome 17q11.2 deletion syndrome, 1.4 Mb | 613675 | 97685, 139474, 636 | AD | 17q11.2 deletion | / | Deletion includes the NFI gene | Neurofibromas, mild facial dysmorphism, intellectual disability, and/or learning disabilities |
| 259 Epileptic encephalopathy, early infantile, 25 | 615905 | 442835 | AR | SLC13A5 | Solute carrier family 13 member 5 | Spasticity, ataxia, choreoathetosis |
| 260 Krabbe disease | 245200 | 487 | AR | GALC | Galactocerebrosidase | Extreme irritability, spasticity, and developmental delay (severe motor and mental deterioration) |
### Table 1 (Continued)

| Group of dental anomaly/name of disease | MIM number | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|------------|-------------|------------|---------|-------|---------------------|
| Krabbe disease, atypical               | 611722     | AR          | PSAP       |         |       |                     |
| Smith-Magenis syndrome                 | 182290     | IC, AD      | RAI1       | Retinoic acid-induced protein 1 | Intellectual disability, hypotonia, speech delay, small ears, conductive hearing loss, esotropia |
| Syndrome de Kohlscütt-Tönz             | 226750     | AR          | ROGDI      | Protein rogdi homolog | Severe global developmental delay, early-onset intractable seizures, spasticity, intellectual disability |
| External auditory canal, bilateral atresia of, with congenital vertical talus | 133705 | /            | /          | /       | Bilateral symmetric subtotal atresia of the external auditory canal |
| Heimler syndrome 1                     | 234580     | AR          | PEX1       | Peroxisome biogenesis factor 1 | Sensorineural hearing loss, nails anomalies |
| Heimler syndrome 2                     | 616617     | AR          | PEX6       | Peroxisome biogenesis factor 6 | Sensorineural hearing deficiencies at birth and later development of progressive retinitis pigmentosa (blindness in adult) |
| Usher syndrome, type 1B               | 276900     | AR          | MYO7A      | Unconventional myosin-VIa | Sensorineural hearing deficiencies at birth and later development of progressive retinitis pigmentosa (blindness in adult) |
| Usher syndrome, type 2A               | 276901     | AR          | USH2A, PDZD7 | Usherin, PDZ domain containing 7 |
| Usher syndrome, type 2C, GPR98/PDZD7 digenic | 605472 | AR, DD      | ADGRV1     | G protein-coupled receptor 98 |
| Usher syndrome, type 3C, GPR98/PDZD7 digenic | 605472 | AR, DD      | PDZD7      | PDZ domain containing 7 |
| Usher syndrome, type 3A               | 276902     | AR          | CLRN1      | Clarin 1 | Combined immunodeficiency with associated or syndromic features: recurrent infections, myopathy, partial iris hypoplasia, autoimmunity, ectodermal dysplasia |
| Immunodeficiency 10                    | 612783     | AR          | STIM1      | Stramal interaction molecule 1 | (Continues) |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes |
|-----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|
| (1) Heart defects                       |                      |                         |             |            |         |       |
| 273 Heart defects                       | 188400, 192430        | 567                     | AD          |            |         |       |
| 274 Deletion, autosomal dominant 36, with dentinogenesis | 605594 | 166260 | AD | DSPP | Dentin sialophosphoprotein |
| 275 Dentin dysplasia type I             | 1653, 99789           | AD                      | DSPP        | VPS4B, SSUH2 | Vacular protein sorting 4 homolog B, SSUH2 | Yang et al., 2016; Xiong et al., 2017 |
| 276 Dentin dysplasia, type II           | 125420               | 1653                    | AD          | DSPP      | Dentin sialophosphoprotein |
| 277 Dentinogenesis imperfecta, shields type II | 125490 | 166260 | AD | DSPP | Dentin sialophosphoprotein |
| 278 Dentinogenesis imperfecta, shields type III | 125500 | 166265 | AD | DSPP | Dentin sialophosphoprotein |
| (2) Eye diseases                        |                      |                         |             |            |         |       |
| 279 Brittle cornea syndrome 1           | 229200               | 90354                   | AR          | ZNF469    | Zing finger protein 469 |
| (3) Bone diseases                       |                      |                         |             |            |         |       |
| 280 Bruck syndrome 1                    | 259450               | 2771                    | AR          | FKBPI0    | Peptidyl-prolyl cis-trans isomerase FKBPI0 |
|                                        |                      |                         |             |            |         |       |

Dentin anomalies (affecting temporary and permanent teeth)

(1) Isolated

| Deafness, autosomal dominant 36, with dentinogenesis | 605594 | 166260 | AD | DSPP | Dentin sialophosphoprotein |
|-----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|
| Dentin dysplasia type I | 1653, 99789 | AD | VPS4B, SSUH2 | Vacular protein sorting 4 homolog B, SSUH2 | Yang et al., 2016; Xiong et al., 2017 |
| Dentin dysplasia, type II | 125420 | 1653 | AD | DSPP | Dentin sialophosphoprotein |
| Dentinogenesis imperfecta, shields type II | 125490 | 166260 | AD | DSPP | Dentin sialophosphoprotein |
| Dentinogenesis imperfecta, shields type III | 125500 | 166265 | AD | DSPP | Dentin sialophosphoprotein |

(2) Eye diseases

| Brittle cornea syndrome 1 | 229200 | 90354 | AR | ZNF469 | Zing finger protein 469 |

(3) Bone diseases

| Bruck syndrome 1 | 259450 | 2771 | AR | FKBPI0 | Peptidyl-prolyl cis-trans isomerase FKBPI0 |

Combined immuno deficiency with associated or syndromic features: immune deficiency due to thymic aplasia/hypoplasia, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability, enamel hypoplasia
| 281 | Caffey disease | 114000 | 1310 | AD | COL1A1 | Collagen type 1 alpha 1 | Inflammatory in nature, with fever and hot, tender swelling of involved bones (mandible, ribs) |
| 282 | Cortical defects, wormian bones, and dentinogenesis imperfecta | 604922 | 166277 | / | / | / | Short, thick arms and fingers, a broad and convex nasal bridge, multiple fractures |
| 283 | Dentin dysplasia with sclerotic bones | 125440 | 99792 | / | / | / | |
| 284 | Ehlers-Danlos syndrome, classic | 130000 | 287 | AD | COL1A1 | Collagen type 1 alpha 1 | Early loss of tooth | Skin hyperextensibility, articular hypermobility, tissue fragility |
| 285 | Ehlers-Danlos syndrome, Arthrochalasia | 130060 | 99875, 99876, 1899 | AD | COL1A1 | Collagen type 1 alpha 1 | | Hip dislocation and extreme joint laxity with recurrent joint subluxations and minimal skin involvement |
| 286 | Ehlers-Danlos syndrome, cardiac-valvular | 225320 | 230851 | AR | COL1A2 | Collagen type 1 alpha 2 | | Bone fragility with normal sclera |
| 287 | Ehlers-Danlos syndrome, Arthrochalasia | 130060 | 99875, 99876, 1899 | AD | COL1A2 | Collagen type 1 alpha 2 | | Hip dislocation and extreme joint laxity with recurrent joint subluxations and minimal skin involvement |
| 288 | Fanconi-renal tubular syndrome 2 | 613388 | 3337 | AD | SLC34A1 | Sodium-dependent phosphate transport protein 2A | Severe rickets and osteopenia, marked hypercalciiuria without renal tubular acidosis |
| 289 | Hypophosphatemic rickets with hypercalciiuria | 241530 | 157215 | AR | SLC34A3 | Sodium-dependent phosphate transport protein 2C | Hypophosphatemia secondary to renal phosphate wasting, radiographic and/or histologic evidence of rickets, limb deformities, muscle weakness, bone pain |
| 290 | Hypophosphatemic rickets, X-linked dominant | 307800 | 89936 | XLD | PHEX | Phosphate-regulating neutral endopeptidase | Rickets with bone deformities, short stature, hypophosphatemia, low renal phosphate reabsorption, normal serum calcium level with hypocalciuria, normal or low serum level of vitamin D [OH]25 (OH)[23, or calcitriol], normal serum level of PTH, and increased activity of serum alkaline phosphatases |
| Group of dental anomaly/ name of disease | Phenotype MIM number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|-----------------------------|-------------|------------|---------|-------|---------------------|
| Hypophosphatemic rickets, autosomal dominant | 193100 | AD | FGF23 | Fibroblast growth factor 23 | Rickets with isolated renal phosphate wasting, hypophosphatemia, inappropriately normal 1,25-dihydroxyvitamin D3 (calcitriol) levels |
| Hypophosphatemic rickets, AR | 241520 | AR | DMP1 | Dentin matrix acidic phosphoprotein 1 | Rickets hypophosphatemia with elevated FGF23 |
| Hypophosphatemic rickets, autosomal recessive, 2 | 613312 | / | ENNRPI | Ectonucleotide pyrophosphatase/phosphodiesterase family member 1 | Rickets hypophosphatemia |
| Hypophosphatemic rickets and hyperparathyroidism | 612089 | AD | / | / | / | Hypophosphatemic rickets and hyperparathyroidism |
| McCune-Albright syndrome, somatic, mosaic | 174800 | 562 | GNAS1 | Protein ALEX | Bone skeleton, skin, and endocrine system anomalies |
| Nephrolithiasis/osteoporosis, hypophosphatemic, 2 | 612287 | AD | SLC9A3R1 | Na(+)/H(+) exchange regulatory cofactor NHE-RF1 | Hypophosphatemia and decreased renal phosphate resorption |
| Osteogenesis imperfecta, type I | 166200 | AD | COL1A1 | Collagen type 1 alpha 1 | Bone fragility and blue sclerae |
| Osteogenesis imperfecta, type II | 166210 | AD | COL1A1 | Collagen type 1 alpha 1 | Perinatal fractures, severe bowing of long bones, undermineralization, and death in the perinatal period due to respiratory insufficiency |
| Osteogenesis imperfecta, type III | 259420 | AD | COL1A1 | Collagen type 1 alpha 1 | Bone fragility with progressive deformity, with normal sclera |
| Osteogenesis imperfecta, type IV | 259420 | AD | COL1A1 | Collagen type 1 alpha 1 | Bone fragility with progressive deformity, with normal sclera |
| Osteogenesis imperfecta, type II | 166210 | AD | COL1A2 | Collagen type 1 alpha 2 | Perinatal fractures, severe bowing of long bones, undermineralization, and death in the perinatal period due to respiratory insufficiency |
| Osteogenesis imperfecta, type III | 259420 | AD | COL1A2 | Collagen type 1 alpha 2 | Bone fragility with progressive deformity, with normal sclera |
| Osteogenesis imperfecta, type IV | 166220 | AD | COL1A2 | Collagen type 1 alpha 2 | Bone fragility with progressive deformity, with normal sclera |


| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|----------------------|--------------------------|-------------|-----------|---------|-------|---------------------|
| Odontochondrodysplasia (Goldblatt syndrome) | 304 184260 | 166272 | AR | TRIP11 | Thyroid hormone receptor interactor 11 | Natal teeth | Spondylometaphyseal dysplasia associated with joint laxity |
| Tumoral calcinosis, hyperphosphatemic familial | 305 211900 | 306661, 53715 | AR | GALNT3 | Polypeptide N-acetylgalactosaminyltransferase 3 | Progressive deposition of basic calcium phosphate crystals in periarticular spaces, soft tissues, and sometimes bone |
| Tumoral calcinosis, hyperphosphatemic familial | 306 211900 | | AR | FGF23 | Fibroblast growth factor 23 | |
| Tumoral calcinosis, hyperphosphatemic familial | 307 211900 | | AR | KL | Klotho | |
| Vitamin D-dependent rickets, type I | 308 264700 | 289157 | AR | CYP27B1 | 25-hydroxyvitamin D-1 alpha hydroxylase, mitochondrial | Enamel anomaly | Intestinal malabsorption of calcium, hypocalcemia, secondary hyperparathyroidism, increased renal clearance of phosphorus, and hypophosphatemia |

Dental eruption/position anomalies

(1) Delayed eruption

(1.1) Isolated

| Failure of tooth eruption, primary | 309 125350 | 412206 | AD | PTHRI | Parathyroid hormone receptor 1 | Severe hypertrichosis, skin abnormalities (hyperlaxity and redundancy), facial dysmorphism, including macrostomia, eyelid deformities, ocular telecanthus, abnormal and low-set ears, bulbous nasal tip with hypoplastic alae nasi, low frontal hairline |

(1.2) Syndromic

| Barber-Say syndrome | 310 209885 | 1231 | AD | TWIST2 | Twist-related protein 2 | Severe hypertrichosis, skin abnormalities (hyperlaxity and redundancy), facial dysmorphism, including macrostomia, eyelid deformities, ocular telecanthus, abnormal and low-set ears, bulbous nasal tip with hypoplastic alae nasi, low frontal hairline |

| Chondrodysplasia, Blomstrand type | 311 215045 | 50945 | AR | PTHRI | Parathyroid hormone receptor 1 | Short limbs, polyhydramnios, hydrops fetalis, facial anomalies, increased bone density, advanced skeletal maturation |

| CODAS syndrome | 312 600373 | 1458 | AR | LONPI | Ion protease homolog, mitochondrial | Developmental delay, craniofacial anomalies, cataracts, ptosis, median nasal groove, hearing loss, short stature, delayed epiphyseal ossification, metaphyseal hip dysplasia, vertebral coronal clefts |
| Group of dental anomaly/name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|---------------------|------------------------|-------------|------------|---------|-------|---------------------|
| Eiken syndrome | 600002 | 79106 | AR | PTH1 | Parathyroid hormone receptor 1 | Retarded ossification |
| Metaphyseal chondrodysplasia, Mark Jansen type | 156400 | 33067 | AD | PTH1 | Parathyroid hormone receptor 1 | Short stature, short bowed limbs, clinodactyly, prominent upper face, small mandible, hypercalcemia and hypophosphatemia |
| Premature aging syndrome, Penttinen type | 601812 | 363665 | AD | PDGFRB | Platelet-derived growth factor receptor beta | Lipoatrophy, epidermal and dermal atrophy, hypertrophic lesions that resemble scars, thin hair, proptosis, underdeveloped cheekbones, marked acroosteolysis |
| Sclerosteosis 1 | 269500 | 3152 | AR | SOST | Sclerostin | Progressive skeletal overgrowth, syndactyly |
| SHORT syndrome | 269880 | 3163 | AD | PIK3R1, IGF1R | Phosphatidylinositol 3-kinase regulatory subunit alpha, insulin growth factor 1 receptor | S = stature; H = hyperextensibility of joints or hernia (inguinal) or both; O = ocular depression; R = Rieger anomaly; T = teething delay |
| Singleton-Merten syndrome 1 | 182250 | 85191 | AD | IFIH1 | Interferon-induced helicase C domain-containing protein 1 | Calcifications of the aorta and aortic and mitral valves, osteoporosis |
| Waardenburg syndrome, type 2E, with or without neurologic involvement | 611584 | 3440, 895 | AD | SOX10 | Transcription factor SOX10 | Pigmentary abnormalities of the hair, skin, and eyes, congenital sensorineural hearing loss |
| Wrinkly skin syndrome | 278250 | 35708, 2834 | AR | ATP6V0A2 | V-type proton ATPase 116 kDa subunit a isoform 2 | Wrinkled skin of the hands, hypotony |

(2) Ectopic eruption
(2.1) Isolated
| Malposition of teeth with or without hypodontia/oligodontia | 189490 | / | / | / | / |

(3) Failure of eruption
(3.1) Isolated
| Impacted teeth, multiple | 308280 | / | / | / | / | Probable underdiagnosed syndrome |
| Group of dental anomaly/name of disease | Phenotype MIM number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|-----------------------------|-------------|------------|---------|-------|---------------------|
| Permanent molars, secondary retention of | 157950 | / | / | / | / | / |

(2.2) Syndromic

| Group of dental anomaly/name of disease | Phenotype MIM number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|-----------------------------|-------------|------------|---------|-------|---------------------|
| GAPO syndrome                          | 230740                      | 2067 AR     | ANTXR1     | Anthrax toxin receptor 1 | Growth retardation, alopecia, progressive optic atrophy, facial dysmorphology |
| Osteopetrosis, autosomal dominant 1    | 607634                      | 2783 AD     | LRPS       | Low-density lipoprotein receptor-related protein 5 | Increased bone density due to impaired bone resorption by osteoclasts |
| Osteopetrosis, autosomal dominant 2    | 166600                      | 53 AD, AR   | CLCN7      | H(+)/Cl(−) exchange transporter 7 | Sclerosis, predominantly involving the spine, pelvis, and skull base. Frailty of bones |
| Osteopetrosis, autosomal recessive 1   | 259700                      | 667 AR     | TIRG1      | V-type proton ATPase 116 kDa subunit a isoform 3 | Macrocephaly and frontal bossing, respiratory problems, increase bone density |
| Osteopetrosis, autosomal recessive 2   | 259710                      | 667 AR     | TNFSF11    | Tumor necrosis factor ligand superfamily member 11 | Genu valgum, anemia, hepatoplenomegaly, and tendency to fracture and mandibular osteomyelitis |
| Osteopetrosis, autosomal recessive 3   | 611490                      | 667 AR     | CLCN7      | H(+)/Cl(−) exchange transporter 7 | Increase bone density |
| Osteopetrosis, autosomal recessive 5   | 259720                      | 85179 AR   | OSTM1      | Osteopetrosis associated transmembrane protein 1 | Increase bone density, |
| Osteopetrosis, autosomal recessive 6   | 611497                      | 210210 AR  | PLEKH1M1   | Pleckstrin homology domain-containing family M | Increase bone density, |
| Osteopetrosis, autosomal recessive 7   | 612301                      | 178389 AR  | TNFRSF11A  | Tumor necrosis factor receptor superfamily member 11A | One family Severe genu valgum |
| Glycogen storage disease Ia (von Gierke disease) | 232200 | AR | G6PC | Glucose-6-phosphatase | Growth retardation, delayed puberty, lactic acidemia, hyperlipidemia, hyperuricemia, hepatic adenomas |
| Glycogen storage disease III | 232400 | AR | AGL | Glycogen debrancher enzyme | Hepatomegaly, hypoglycemia and growth retardation, muscle weakness |
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|-------------------|
| 336 Glycogen storage disease Ixa          | 306000               |                         | XLR         | PHKA2      | Alpha-2 subunit of hepatic phosphorylase kinase | Hepatomegaly, hypoglycemia and growth retardation, muscle weakness in infancy. Adults are asymptomatic |
| (4) Premature loss of teeth              |                      |                         |             |            |         |       |                   |
| 337 Hajdu-Cheney syndrome                | 102500               |                         | AD          | NOTCH2     | Neurogenic locus notch homolog protein 2 | Facial dysmorphology, bowing of the long bones, vertebral anomalies, acro-osteolysis of phalanges of hand and feet, short stature |
| 338 Hypophosphatasia, adult              | 146300               | 247676, 436, 247685     | AR, AD      | ALPL       | Alkaline phosphatase, tissue-nonspecific isozyme | Mild bone fragility, osteomalacia, pseudo-fracture, history of rickets |
| 339 Hypophosphatasia, childhood          | 241510               | 247667, 436             | AR          | ALPL       | Alkaline phosphatase, tissue-nonspecific isozyme | Defective bone mineralization and biochemically, short stature, skeletal deformities, motor impairment, fatigue easily |
| 340 Hypophosphatasia, infantile          | 241500               | 436, 247651, 247623     | AR          | ALPL       | Alkaline phosphatase, tissue-nonspecific isozyme | Defective bone mineralization and biochemically before 6 month, rickets, failure to thrive, hypotonia |
| 341 Mandibuloacral dysplasia             | 248370               | 2457, 90153             | AR          | LMNA       | Lamin | Growth retardation, facial dysmorphism, skeletal abnormalities (progressive osteolysis of the distal phalanges and clavicles), pigmented skin changes |
| 342 Mandibuloacral dysplasia with type B lipodystrophy | 608612 | 2457, 90154 | AR | ZMPSTE24 | CAAX prenyl protease 1 homolog | Growth retardation, facial dysmorphism, progressive acral osteolysis, mottled or patchy pigmentation, skin atrophy, and partial or generalized lipodystrophy |
| 343 Odontohypophosphatasia               | 146300               | 247676, 436, 247685     | AR, AD      | ALPL       | Alkaline phosphatase, tissue-nonspecific isozyme | Mild bone fragility |
| 344 Osteolysis, familial expansile       | 174810               | 85195                   | AD          | TNFRSF11A  | Tumor necrosis factor receptor superfamily member 11A (RANK) | Bone remodeling with osteolytic lesions, early hearing loss, osteopenia |

(Continues)
## Table 1 (Continued)

| Group of dental anomaly/name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|-------------------------|-------------|------------|---------|-------|-------------------|
| Singleton-Merten dysplasia/syndrome    | 182250               | 85191                   | AD          | IFIH1 (MDA5) | Interferon-induced helicase C domain containing protein 1 | Auto-inflammatory disorder: progressive calcification of the thoracic aorta with stenosis, osteoporosis and expansion of the marrow cavities in hand bones, generalized muscle weakness and atrophy, chronic psoriasiform skin eruptions, delayed primary tooth exfoliation and permanent tooth eruption, truncated tooth root formation, early-onset periodontal disease, severe root and alveolar bone resorption, abnormal mineralization |
| Odontomicrochial dysplasia              | 601319               | 1811                    | AR          | /          | /       | One family | Short stature, slow growing, nail alteration |
| Hyper-IGE syndrome (HIES) (Job syndrome)| 147060               | 2314                    | AD          | STAT3      | Signal transducer and activator of transcription 3 | Combined immunodeficiency with associated or syndromic features: chronic eczema, recurrent staphylococcal infections, pulmonary aspergillus, mucocutaneous candidiasis, hyperextensible joints, increased serum IgE, hyperesinophilia, bone fracture, scoliosis, facial dysmorphology (facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge, fleshy nasal tip, prognathism), reduced resorption of primary tooth roots leading to prolonged retention of primary teeth and delayed eruption of permanent teeth |
| Hyper-IGE recurrent infection syndrome, autosomal recessive | 243700               | 217390                  | AR          | DOCK8      | Dedicator of cytokinesis protein 8 | Chronic eczema, recurrent staphylococcal infections, increased serum IgE, eosinophilia, facial dysmorphology |
| Group of dental anomaly/ name of disease | Phenotype | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|-----------|--------------------------|-------------|------------|---------|-------|---------------------|
| Periodontal and gingival anomalies |           |                          |             |            |         |       |                     |
| (1) Gingival overgrowth/enlargement |           |                          |             |            |         |       |                     |
| (1.1) Isolated                        |           |                          |             |            |         |       |                     |
| 349 Fibromatosis, gingival, 1          | 135300    | 2024                     | AD          | SOS1       | Son of sevenless homolog 1 |       |                     |
| 350 Fibromatosis, gingival, 2          | 605544    | /                        | /           | /          | /       | /     |                     |
| 351 Fibromatosis, gingival, 3          | 609955    | /                        | /           | /          | /       | /     |                     |
| 352 Fibromatosis, gingival, 4          | 611010    | /                        | /           | /          | /       | /     |                     |
| (1.2) Syndromic                       |           |                          |             |            |         |       |                     |
| 353 Ehlers-Danlos syndrome, Dermatosparaxis | 225410  | 1901                     | AR          | ADAMTS2    | A disintegrin and metalloproteinase with thrombospondin motifs 2 | Oligodontia, dentin defect | Severe joint hyperr extensibility and mild stretchability and bru isability of the skin |
| 354 Ehlers-Danlos syndrome, vascular | 130050    | 286                      | AD          | COL3A1     | Collagen 3 | Papyraceous aspect of the gingiva (Ferre et al., 2012) | Joint and skin laxity, proneness to spontaneous rupture of bowel and large arteries |
| 355 Epileptic encephalopathy, early infantile, 31 | 616346  | 2382,442835              | AD          | DNMI       | Dynamin 1 | Three patients | Epileptic encephalopathy |
| 356 Hyaline fibromatosis syndrome     | 228600    | 2028                     | AR          | ANTXR2     | Anthrax toxin receptor 2 | Abnormal growth of hyalized fibrous tissue usually affecting subcutaneous regions on the scalp, ears, neck, face, hands, and feet |
| 357 Histiocytosis-lymphadenopathy plus syndrome | 602782  | 168569, 158014           | AR          | SLC29A3    | Equilibrative nucleoside transporter 3 | Histiocytosis and lymphadenopathy with or without cutaneous, cardiac, and/or endocrine features, joint contractures, and/or deafness |
| 358 Frank-ter Haar syndrome           | 249420    | 1266                     | AR          | SH3PD2B    | SH3 and PX domain-containing protein 2B | Brachycephaly, wide fontanels, prominent forehead, hypertelorism, prominent eyes, macrocornea with or without glaucoma, full cheeks, small chin, bowing of the long bones, flexion deformity of the fingers |
| 359 Hypertrichosis terminalis, generalized, with or without gingival hyperplasia | 135400  | 2026                     | AR          | 17q24.2-q24.3 microdeletion or microduplication / | ABCAS5 gene concerned | Hypertrichosis, hirsutism | (Continues) |
| Group of dental anomaly/ name of disease | Orphanet number (ORPHA) | MIM number | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|-------------------------|------------|-------------|------------|---------|-------|-------------------|
| Hypertrichosis universalis congenita, Ambras type | 185701 | 1023, 2222 | AD | 8q22 | / | / | Hypertrichosis |
| Hypertrichosis, congenital generalized | 307150 | 2222, 79495 | XLD | / | / | / | Hypertrichosis |
| Macrocephaly, alopecia, cutis laxa, and scoliosis | 613075 | 217335 | AR | RIN2 | Ras and Rab interactor 2 | Macrocephaly, alopecia, cutis laxa, scoliosis, sagging skin |
| Macrocephaly, alopecia, cutis laxa, and scoliosis | 613075 | 217335 | AR | RIN2 | Ras and Rab interactor 2 | Macrocephaly, alopecia, cutis laxa, scoliosis, sagging skin |
| Main manifestations | | | | | | | |
| Subcutaneous or soft tissue nodules of the skin of the head, neck, and trunk, skeletal and muscular lesions | | | | | | | |
| Robinow syndrome, autosomal dominant 1 | 180700 | 3019 | / | / | / | / | Cherubism, epilepsy, intellectual disability, hypertrichosis, stunted growth |
| Robinow syndrome, autosomal dominant 2 | 616331 | 3107, 97360 | AD | WNT5A | Protein Wnt-5a | Fetal face, mesomelic limb shortening, hypoplastic external genitalia in males, renal and vertebral anomalies |
| Robinow syndrome, autosomal dominant 2 | 616331 | 3107, 97360 | AD | WNT5A | Protein Wnt-5a | Fetal face, mesomelic limb shortening, hypoplastic external genitalia in males, renal and vertebral anomalies |
| Rutherfurd syndrome | 180900 | 2709 | / | / | / | / | Corneal dystrophy, inconstat intellectual disability |
| Fibromatosis, gingival, with hypertrichosis and intellectual disability | 605400 | / | / | / | / | / | Intellectual disability, epilepsy, short fingers, hirsutism, bulbous short nose |
| Fibromatosis, gingival with distinctive facies | 228560 | 2025 | / | / | / | One family | Macrocephaly, bushy eyebrows with synophrys, hypertelorism, flattened nasal bridge and hypoplastic nares, cupid-bow mouth |
| Fibromatosis gingival with progressive deafness syndrome | 135550 | 2027 | / | / | / | / | Progressive sensorineural hearing loss |
| Acroosteolysis dominant type (Hadju-Cheney syndrome) | 102400, 102500 | 955 | AD | NOTCH2 | Neurogenic locus notch homolog protein 2 | Acroosteolysis of distal phalanges, craniofacial dysmorphism, hypertelorism, telanchnus, micrognathia, bone anomalies, early loss of teeth |

(Continues)
### TABLE 1  (Continued)

| Group of dental anomaly/ name of disease | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|------------------------------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| Phenotype number | MIM number | | | | | |
| 372 Zimmermann-Laband syndrome 1 | 135500 | 3473 | AD | KCNH1 | Potassium voltage-gated channel subfamily H member 1 | Dysplastic or absent nails, the absence of the distal phalanges, scoliosis, hepatosplenomegaly, hirsutism, abnormalities of the cartilage of the nose and/or ears |

(2) Periodontal disease

(2.1) Isolated

| Periodontitis, chronic | 260950 | / | / | / | / | The terms chronic, juvenile and aggressive are no more used in the new classification of periodontal disease. They are included in only one term which is periodontitis. Papapanou et al., 2018 |

| Periodontitis 1, juvenile | 170650 | / | AR | CTSC | Cathepsin C |

| Periodontitis, aggressive 2 | 608526 | / | / | / | / |

(2.2) Syndromic

| Dyskeratosis congenita, X-linked | 305000 | 1775, 3322 | XLR | DKCI | H/ACA ribonucleoprotein complex subunit 4 | Combined immunodeficiency with associated or syndromic features: triad of dysplastic nails, lacy reticular pigmentation and skin atrophy (neck and upper chest) + oral leukoplakia/ increased risk for progressive bone marrow failure and risk to develop myelodysplastic syndrome or acute myelogenous leukemia / increased risk for solid tumors (squamous cell carcinoma of head and neck, anogenital cancer) / developmental delay, short stature, microcephaly, blepharitis, periodontal disease, taurodontism, decreased teeth/ root ratio, esophageal stenosis, liver disease, urethral stenosis, osteoporosis, avascular necrosis of femur and/or humerus, premature hair graying/alopecia, or abnormal eyelashes |

(Continues)
| Group of dental anomaly/ name of disease | Phenotype number (MIM) | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|-----------------------------------------|------------------------|-------------------------|-------------|------------|---------|-------|---------------------|
| 377 Dyskeratosis congenita, autosomal recessive 1 | 224230 | 1775 | AR | NOP10 | H/ACA ribonucleoprotein complex subunit 3 |
| 378 Dyskeratosis congenita, autosomal dominant 1 | 127550 | 1775 | AD | TERC | Non coding RNA |
| 379 Dyskeratosis congenita, autosomal dominant 2, autosomal recessive 4 | 613989 | 1775 | AD, AR | TERT | Telomerase reverse transcriptase |
| 380 Ehlers-Danlos syndrome, periodontal | 130080 | 75392 | AD | C1R | Complement C1r subcomponent isoform 2 | Joint hypermobility and skin abnormalities |
| 381 Ehlers-Danlos syndrome, periodontal | 617174 | 75392 | AD | C1S | Complement C1s subcomponent isoform 2 | Joint hypermobility and skin abnormalities |
| 382 Haim-Munk syndrome | 245010 | 2342 | AR | CTSC | Cathepsin C | Palmoplantar keratoderma, severe early-onset periodontitis with early tooth loss, arachnodactyly, acroosteolysis, atrophic changes of the nails, radiographic deformity of the fingers, onychogryphosis, pes planus, increased susceptibility to infections. Mutations in the same gene cause the clinically related disorder Papillon-Lefèvre syndrome. |
| 383 Hermansky-Pudlak syndrome 2 | 608233 | 183678 | AR | AP3B1 | AP-3 complex subunit beta-1 | Platelet defects and oculocutaneous albinism |
| 384 Hypotrichosis, osteolysis, periodontitis-palmoplantar keratoderma syndrome | 607658 | 307936 | / | / | / | Hypotrichosis, striate palmoplantar keratoderma, onychogryphosis, acroosteolysis, psoriasis-like skin lesions |
| 385 Kindler syndrome | 173650 | 306539 | AR | FERM1 | Fermitin family homolog 1 (kindlin1 gene) | Epidermolysis bullosa: congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling |
| 386 Leukocyte adhesion deficiency type 1 (LAD1) | 116920 | 99842 | AR | ITGB2 | Integrin beta 2 (CD18) | Congenital defect of phagocyte function: recurrent, life-threatening bacterial infections (skin, mouth, respiratory tract), delayed umbilical cord separation, severe periodontitis with early tooth loss, lack of pus formation and wound healing |

(Continues)
| **Group of dental anomaly/name of disease** | **Phenotype number (MIM)** | **Orphanet number (ORPHA)** | **Inheritance** | **Gene/locus** | **Protein** | **Notes** |
|-------------------------------------------|---------------------------|-----------------------------|-----------------|---------------|------------|----------|
| Leukocyte adhesion deficiency type 2 (congenital disorder of glycosylation type Ib, LAD2) | 266265 | 99843 | AR | SLC35C1 | Solute carrier family 35, member C1 (GDP-fucose transporter 1) | Congenital defect of phagocyte function; mild LAD type 1 features with severe growth retardation, severe intellectual deficit, Bombay (hh) blood group, facial dysmorphism (depressed nasal bridge) |
| Leukocyte adhesion deficiency type 3 (LAD3) | 612840 | 99844 | AR | FERM3 | Fermitin family member 3 | Congenital defect of phagocyte function; LAD type 1 phenotype with severe bleeding disorder |
| Severe congenital neutropenia type 1, autosomal dominant (SCN1) | 202700 | 486 | AD | ELANE | Neutrophil elastase | Congenital defects of phagocyte number; Severe congenital neutropenia, severe recurrent bacterial infections, increased risk of myelodysplastic syndrome and leukemia, severe periodontitis with early tooth loss, oral ulcers |
| Severe congenital neutropenia type 3, autosomal recessive (Kostmann syndrome, SCN3) | 610738 | 99749 | AR | HAX1 | HCLS1-associated protein X1 | Congenital defects of phagocyte number; Severe congenital neutropenia, severe recurrent bacterial infections, increased risk of myelodysplastic syndrome and leukemia, severe periodontitis with early tooth loss, oral ulcers, cognitive and neurological defects |
| Glycogen storage disease due to glucose-6-phosphatase deficiency type Ib | 232220 | 79259 | AR | SLC37A4 | Glucose 6-phosphate translocase | Recurrent infections and neutropenia, higher prevalence of severe periodontitis |
| Neutropenia, chronic familial | 162700 | / | / | / | / | Severe congenital neutropenia |
| Chronic granulomatous disease | 306400, 233700, 233690, 233710, 613960 | 379 | AR, XL | CYBA, CYBB, NCF1, NCF2, NCF4 | Primary immunodeficiency, recurrent bacterial and fungal infections, development of granulomas |
| Plasminogen deficiency | 217090 | 722 | AR | PLG | Plasminogen | Impaired extracellular fibrinolysis, pseudomembranes on mucosa during wound healing |
| Cohen syndrome | 216550 | 193 | AR | VPS13B | Vacuolar protein sorting 13B | Microcephaly, characteristic facial features, hypotonia, non-progressive intellectual deficit, myopia and retinal dystrophy, neutropenia and truncal obesity |
| Group of dental anomaly/ name of disease | Phenotype MIM number | Orphanet number (ORPHA) | Inheritance | Gene/locus | Protein | Notes | Main manifestations |
|----------------------------------------|----------------------|--------------------------|-------------|------------|---------|-------|---------------------|
| Chediak-Higashi syndrome               | 214500               | 167                      | AR          | LYST       |         |       | Disease of immune dysregulation: partial oculocutaneous albinism, severe immunodeficiency (recurrent bacterial infections), hemophagocytic lymphohistiocytosis, increased bleeding tendency, neurological dysfunction, lymphoproliferative disorder, severe periodontal disease |
| Hereditary angioedema                  | 106100, 610618       | 91378                    |             | SERPING1   | C1 inhibitor |       | Subcutaneous or submucosal edemas |
| Pachyonychia congenita 1               | 167200               | 2309                     | AD          | KRT16, KRT6A, KRT6B, KRT6C | Keratin 16 et 6 |       | Hypertrophic nail dystrophy, painful and highly debilitating plantar keratoderma, oral leukokeratosis, epidermal cysts |
| Pachyonychia congenita 2               | 167210               | AD                       | KRT17       | Keratin 17 |         |       | Congenital defect of phagocyte function: ectodermal dysplasia with palmoplantar keratoderma, severe early-onset periodontitis with early tooth loss, increased susceptibility to cutaneous and systemic infections |
| Papillon-Lefevre syndrome              | 245000               | 678                      | AR          | CTSC       | Cathepsin C |       | Multiple nevoid basal-cell epitheliomas, jaw cysts, and bifid rib |
| Basal cell nevus syndrome              | 109400               | 377                      | AD          | PTCH2      | Protein patched homolog 2 |       | Multilocular cystic changes in the mandible and maxilla |
| Basal cell nevus syndrome              | 109400               | AD                       | PTCH1       | Protein patched homolog 1 |         |       | Nevus psiloliparus, a well-demarcated, alopecic fatty tissue nevus on the scalp |
| Cherubism                              | 118400               | 184                      | AD          | SH3BP2     | SH3 domain-binding protein 2 |         |         |
| Encephalocraniocutaneous lipomatosis   | 613001               | 2396                     | IC          | FGFR1, KRA5 | Fibroblast growth factor receptor 1, GTPase Kras |         |         |
Nosology of genetic dental disorders

The oral rare disease expert group established a classification of dental disorders based on personal clinical observations collected across the national network and literature data. OMIM, Orphanet, and PubMed (Canese & Weis, 2002) were searched up to December 2018. The PubMed search was performed using as search terms: “dental agenesis,” “supernumerary tooth,” “microdontia,” “macrodontia,” “enamel dysplasia,” “dentin dysplasia,” “dental eruption anomaly,” “gingival overgrowth,” “periodontal disease,” and “dental disorder.” Only English-language publications were accepted. Developmental defects were recorded and grouped in eight clusters of dental disorders (dental agenesis, supernumerary teeth, morphology dental anomaly [size and shape], enamel anomaly, dentin anomaly, anomaly of dental eruption, periodontal and gingival anomalies, and tumor-like disorders). In each group, pathologies were subdivided into “isolated” or “syndromic.” Syndromes were classified by their main clinical medical features (skin, eye, bone, endocrine organs, kidneys, cranio-facial, cancer, and intellectual disability). If dental anomalies were insufficiently described in OMIM, original articles were analyzed. The classification includes the name of the pathology, OMIM codes, Orpha numbers, gene(s) involved, protein(s), and the other main medical manifestations (Table 1). Notes were added if complementary information was needed. If OMIM and/or Orphanet number was not available, essential references were added.

The criteria for including a disorder were:

1. The presence of dental anomalies (Supplementary Data Table S1)
2. Published in a peer-reviewed journal, in one or more of three dedicated textbooks (Bloch-Zupan et al., 2012; Hall, 1994; Hennekam et al., 2010) and/or listed in OMIM and/or Orphanet database; unpublished observations were not included.
3. Either a proven molecular genetic basis (variants; linkage analyses) or internationally accepted clinical entities due to distinctive clinical manifestations observed in multiple individuals.

3 | RESULTS

3.1 | Defining dental anomalies

3.1.1 | Anatomy of teeth and oral mucosa

General

The oral region includes the maxillae, the mandible, muscles, glands, and other structures related to the oral functions. The oral cavity belongs to the oral region and is the space bounded superiorly by the palate, laterally by the cheeks, anteriorly by the lips, inferiorly by the floor of the mouth, and posteriorly limited by the uvula and the palato-glossal arches and communicates with the oropharynx. The oral cavity contains oral mucosa, tongue, teeth, periodontium, and alveolar processes surrounding dental roots (Figure 1).
Anatomy

Oral Mucosa. The oral mucosa has been defined before as epithelium covering the inner aspect of the oral cavity (Carey et al., 2009). This refers only to the lining epithelium. The oral mucosa is composed of two layers: the epithelium and associated connective tissue, separated by a basal membrane. There are three types of oral mucosa: lining, masticatory, and specialized. Lining mucosa covers the oral cavity except for the dorsal surface of the tongue, hard palate, and teeth bearing area (namely gingiva). The epithelium is non-keratinized, and its connective tissue is not tightly bound but quite mobile. Lining mucosa is separated from gingiva by the mucogingival junction (Figure 2). Masticatory mucosa comprises gingiva and covers hard palate, its epithelium is keratinized, and the connective tissue is strongly linked to underlying structures, mainly bone. The dorsal surface of the tongue is covered by a specialized mucosa, which contains papillae (filiform, fungiform, and circumvallate) and taste buds.

Tooth. Teeth are organs usually attached in a row to each jaw and include various hard and soft tissues (enamel, dentin, pulp, and cementum) (Figure 3) (Nanci, 2012). Their anatomical overall shape is adapted to their functions. Anatomically, teeth can be divided into the crown and the root by the cervical margin. The crown is the part of the tooth that is visible in the oral cavity. The root is surrounded by the periodontium. The dentin pulp complex constitutes the main structure of the tooth, covered by enamel in the crown and cementum in the root.

Dentition. Humans have two dentitions: a deciduous (primary) dentition and a permanent (secondary) dentition, which replaces the former one. The shape and position of teeth follow a specific pattern. Deciduous dentition accounts for 20 teeth (two incisors, one canine, and two molars per quadrant), whereas permanent dentition accounts for 32 teeth (two incisors, one canine, two premolars, three molars per quadrant). The first teeth erupt at around 6 months of age and the last one at around 18 years old. Dental development, patterning, and eruption timing and sequence have been described in detail elsewhere (Lunt & Law, 1974; McDonald, Avery, & Dean, 2004).

A numeration system designs human deciduous and permanent teeth according to their type and location following the FDI two digits (“FDI Director calls on more countries to adopt the FDI two-digit tooth-numbering system,” 1988) and ISO 3950:2016 (Dentistry – Designation system for teeth and areas of the oral cavity) recommendations (Figure 4).

Incisor. Teeth located in the anterior part of the arches of maxilla and mandible. The typical crown shape is approximately rectangular. They have a single root. Two incisors (one central and one lateral from the midline) exist per quadrant (Figure 4).

Canine. Teeth located between the incisors and the molars in deciduous teeth and between the incisors and the premolars in permanent teeth. The typical crown shape is pointed. They have a single root. One canine exists per quadrant (Figure 4).

Premolar. Teeth located between the canines and the molars in the permanent dentition. Two premolars exist per quadrant. The occlusal surface of the crown is composed of two cusps (one labial and one lingual). They have one or two roots (Figure 4).

Molar. Teeth located in the posterior part of the dental arches of maxilla and mandible. In the deciduous dentition, two molars exist which will be replaced by premolars. In the permanent dentition, three molars exist appearing at around 6 years of age for the first permanent molars, 12 years of age for the second permanent molars and at adulthood for the third permanent molars (or wisdom teeth). The typical shape is with multiple cusps and multiple roots. Maxillary molars have two vestibular cusps and one lingual cusp. Mandibular molars have three vestibular cusps and two lingual cusps (Figure 4). Maxillary molars have three roots, two vestibular, and one palatal. Mandibular molars have two roots, one mesial, and one distal. Their shape and size may vary according to sex, ethnicity, and geography.
FIGURE 3  Major anatomical landmarks of the teeth (see text) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4  (a) Teeth in the dental arches, the odontogram is from D(4)/phenodent database. (b) This table represents the normal mesiodistal and standard deviation (M=Male; F=Female) [Color figure can be viewed at wileyonlinelibrary.com]
**Enamel.** Hard acellular structure covering tooth crown. Enamel is the most mineralized material (98%) in the human body, secreted by ameloblasts. Ameloblasts disappear as the tooth erupts within the oral cavity. Enamel is able to neither regenerate nor repair. Enamel is translucent and appears to have a color that varies from white to light yellow depending of the color of the dentin. The surface is smooth and glossy (Figure 3).

**Dentin.** Dentin is a mineralized connective tissue forming the dental crown and root. Dentin is a vital tissue, less mineralized than enamel, and has the capacity to repair. Odontoblasts are the dentin forming cells and are located in the dental pulp periphery just below dentin. Odontoblasts extend a long cytoplasmic process radially from the pulp to the dentino-enamel and dentino-cemental junctions inside canaliculi; these are called dentin tubuli (Figure 3).

**Dental pulp.** Soft connective tissue occupying the inner portion of the tooth, both in the crown (pulp chambers) and the root canals covered by dentin. The dental pulp consists of fibroblasts, odontoblasts, undifferentiated ectomesenchymal cells, macrophages and other immunocompetent cells, blood vessels, and nervous fibers (Figure 3).

**Cementum.** Mineralized connective tissue covering the dental root. The cementum allows anchoring of the fibers of the periodontal ligament. Cementum is secreted by cementoblasts, which may be, later on, embedded in the cementum. Cementum can be acellular (along the two third coronal portion of the root) and cellular (in the apical and interradicular part of the root) (Figure 3).

**Cusp.** Eminence of the occlusal surface of a tooth. Canines possess a single cusp, premolars two (bicuspids), and molars three to five cusps (Figures 3 and 4).

**Mamelons.** Small tubercules on the incisal edge when the incisors erupt. Mamelons typically disappear or decrease in size as they get worn away by mastication (Figure 5).

**Periodontium.** The periodontium encompasses the cementum, periodontal ligament, alveolar bone, and gingiva (Figure 3).

**Periodontal ligament.** Connective tissue attaching the tooth root to the alveolar bone of the maxillae or mandible (Figure 3).

**Gingiva.** Gingiva or gum is the part of the oral mucosa covering the teeth bearing area of the jaw (alveolar processes). Attached gingiva, free gingiva, and marginal gingiva (Figure 1).

**Measurements of the teeth**
Measure of teeth was reported giving mean value for mesiodistal diameters, labio- or bucco-lingual diameter, length of root, and length of crown. The size of tooth varies across ethnic groups (Black, 1890; Lavelle, 1972) (Figure 4).

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**4 | DEFINITIONS**

**4.1 | Tooth, anomaly**

**4.1.1 | Definition**
Alteration in the number, shape, size, or structure, in the chronology of eruption or the alignment in the dental arch, of a single tooth or multiple teeth. **Objective** or **subjective**.

**4.1.2 | Comments**
An anomaly can be explained as a malformation, a dysplasia, a deformation or disruption, and classifying a dental anomaly as such helps in understanding etiology and pathogenesis (Hennekam et al., 2013). Teeth anomalies can affect the tooth crown, tooth root, or both. For root anomalies, diagnosis requires typically radiographic examinations as well.

**Replaces:** Dental defect  
**Synonym:** Dental anomaly  
Dental anomaly: see **Tooth, anomaly**.

**4.2 | Tooth, missing**

**4.2.1 | Definition**
Apparent absence of one or more teeth during the visual inspection of the oral cavity. **Objective**.

**4.2.2 | Comment**
The tooth may appear to be absent due to a disturbed eruption, failure to develop, or loss of teeth. Age-related physiological sequential eruption should be taken into account during evaluations.
Synonym: Tooth, reduced number
Tooth, reduced number: see Tooth, missing.

4.3 | Teeth, agenesis

4.3.1 | Definition

The absence of one or more teeth from the normal series by a failure to develop (Figures 6–8). Objective.

4.3.2 | Comments

Teeth agenesis needs to be confirmed by X-rays. Teeth agenesis encompasses hypodontia, oligodontia, and anodontia. The total number and the type of teeth missing should be added to the description, using the FDI nomenclature. The clinical absence of a tooth due to a disturbed eruption should not be termed teeth agenesis but a missing tooth.

Synonym: Dental agenesis
Dental agenesis: see Teeth, agenesis.

4.4 | Hypodontia

4.4.1 | Definition

The absence of five or less teeth from the normal series by a failure to develop (Figure 6). Objective.

4.4.2 | Comments

Hypodontia needs to be confirmed by X-rays. The total number and the type of missing teeth should be added to the description, using the FDI nomenclature (“FDI Director calls on more countries to adopt the FDI two-digit tooth-numbering system,” 1988; Peck & Peck, 1993). The terms hypodontia and oligodontia have been used interchangeably in literature but these define two different clinical entities. Hypodontia has been used to define exclusively the absence of permanent teeth and excluding third molars, but the absence of any deciduous and permanent teeth, including third molars, should be called hypodontia as well. Hypodontia in the permanent dentition (other than third molars) affects 2–8% of the general population (Polder, Van’t Hof, Van der Linden, & Kuijpers-Jagtman, 2004). The permanent dentition is more often concerned but when it affects the deciduous dentition, the permanent dentition is usually also affected (Polder et al., 2004). Third molars agenesis occurs in up to 10–30% within the general population. Hypodontia of a permanent tooth is often associated with persistence of the deciduous predecessor and may be associated with other dental anomalies such as delayed eruption, infraocclusion of deciduous molars (if premolars are involved), microdontia, ectopic tooth eruption, short roots, taurodontism, tooth

FIGURE 6  Hypodontia—panoramic radiography of a 7 years old child showing four dental agenesis (see the stars second left maxillary premolar, mandibular central incisors, mandibular second left premolar). Deciduous and permanent molars are taurodont. Maxillary central incisor presents a screwdriver shape anomaly

FIGURE 7  Oligodontia—patient with oligodontia (missing 12 permanent teeth see the stars: maxillary first and second premolars, mandibular second premolars, second molars, and four wisdom teeth). Abnormalities of tooth shape and tooth structure (enamel hypoplasia) are also seen on upper permanent central incisors [Color figure can be viewed at wileyonlinelibrary.com]
rotation, or *enamel hypocalcification*. These signs should be assessed and coded separately. The clinical absence of a tooth due to a disturbed eruption should not be termed teeth agenesis but a *missing tooth*.

### 4.5 Oligodontia

**4.5.1 Definition**

The absence of six or more teeth from the normal series by a failure to develop. (Figure 7). Objective.

**4.5.2 Comments**

Oligodontia needs to be confirmed by X-rays. The number and the type of teeth missing should be added to the description using the FDI nomenclature (Peck & Peck, 1993) (“FDI Director calls on more countries to adopt the FDI two-digit tooth-numbering system,” 1988). The terms *oligodontia* and *hypodontia* have been used interchangeably in literature, but these define two different clinical entities if considering the number of missing teeth. Maxillary lateral incisor and second premolar are more commonly part of oligodontia (Fournier et al., 2018), maxillary second premolars, mandibular incisor, and maxillary and mandibular first premolars, and second molars are less frequently absent. Canines, maxillary central incisor, and first molars are the more conserved teeth. Agenesis of a permanent tooth is often associated with persistence of the deciduous predecessor and may be associated with other dental anomalies such as delayed eruption, infraocclusion of deciduous molars (if premolars are involved), microdontia, ectopic teeth, short roots, taurodontism, tooth rotation, or *enamel hypocalcification*. These signs should be assessed and coded separately. Isolated oligodontia affects 0.1% of the population (Polder et al., 2004). The clinical absence of a tooth due to a disturbed eruption should not be termed teeth agenesis but a *missing tooth*.

### 4.6 Anodontia

**4.6.1 Definition**

The absence of all teeth from the normal series by a failure to develop. (Figure 8). Objective.

**4.6.2 Comments**

Anodontia needs to be confirmed by X-rays. True anodontia is an extremely rare condition.

### 4.7 Solitary median maxillary central incisor

**4.7.1 Definition**

A single maxillary central incisor positioned in the midline with morphological symmetry of the crown and bordered by lateral incisors (Figure 9). Objective.

**4.7.2 Comments**

The tooth differs from a normal central incisor in the symmetric formation of the crown. The tooth is present in both deciduous and permanent dentition. Solitary/single median maxillary central incisor syndrome (SMMC) indicates the presence of a single median maxillary central incisor together with other midline defects of development (Hall, 2006). A single maxillary central incisor not positioned in the midline indicates agenesis of the contralateral central incisor and can be differentiated furthermore by the morphology of the crown. A diagnosis of a solitary median maxillary central incisor typically requires X-rays examinations.
4.8 | Mesiodens

4.8.1 | Definition
A supernumerary tooth between the maxillary central incisors (Figure 10). Objective.

4.8.2 | Comments
Mesiodens is the most common supernumerary tooth. Typically, they are small. They are usually conical in shape but may have heterogeneous forms. Mesiodens may remain unerupted and cause failure of a permanent incisor to erupt. Mesiodens may develop in an inverted position (flipped $180^\circ$).

Tooth, extra: see Tooth, supernumerary.

Tooth, increased number: see Tooth, supernumerary.

4.9 | Tooth, supernumerary

4.9.1 | Definition
The presence of one or more teeth additional to the normal number (Figure 11). Objective.

4.9.2 | Comments
Age-related physiological sequential eruption should be taken into account during evaluation. The type and the location of the additional tooth/teeth should be added to the description. Supernumerary teeth are uncommon (in 0.21% of deciduous dentitions and in 0.9% of permanent dentitions) (Lagana et al., 2017), and often abnormal positioning of a normal number of teeth is wrongly classified as supernumerary teeth. Supernumerary teeth are most frequent in the upper maxilla, and typically, a single additional tooth is present. We discourage the use of distodens, distomolars (an extra fourth molar posterior to the third molar), paramolars (supernumerary tooth in the molar region) but rather to mention the presence of the supernumerary tooth mesial to or distal to a tooth from the normal series. Diagnosing a supernumerary tooth may require radiographic examination. A supernumerary tooth present between the maxillary central incisors is called mesiodens.

Synonym: Tooth, extra teeth; Hyperdontia; Tooth, increased number.

4.10 | Enamel, pearls

4.10.1 | Definition
Small nodules of enamel on the root of a tooth (Figure 12). Subjective.

4.10.2 | Comments
Enamel pearls can typically not be seen on X-rays but need direct visualization. The pearls can be present on the surface of the dentine or cement of deciduous teeth, with a frequency of 33% (Arys & Dourov, 1987) or on the roots of maxillary molars, with a frequency of 1.2% (Chrcanovic, Abreu, & Custodio, 2010).
4.11 | Cusps, supernumerary

4.11.1 | Definition

Additional cusps of a dental crown. (Figure 13). Objective.

4.11.2 | Comments

Supernumerary cusps can occur on any tooth with cusps. They are frequently seen in patients with other dental anomalies (Herrera-Atoche et al., 2017). Prevalence varies by geographical region (Yamunadevi et al., 2015). A tubercle on the lingual surface of the maxillary first permanent molar is sometimes referred to as a Carabelli cusp (Carabelli, 1844) (Poornima, Kirthiga, Sasalwad, & Nagaveni, 2016; Tinoco, Lima, Delving, Francesquini Jr., & Daruge Jr., 2016). A supernumerary cusp on the lingual or palatal side of anterior teeth is called Talon cusp, and an additional cusp on the occlusal surface of a premolar is called Leung cusp.

Replaces term: Tuberculum paramolare
Synonym: Cusp, extra; Cusp, additional cusp; Mulberry molar
Cingulum, prominent: see Talon cusp.
Cusp, additional: see Cusp, supernumerary.
Cusp, extra: see Cusp, supernumerary.
Dens evaginatus: see Leung cusp.
Dens evaginatus: see Talon cusp.
Eagle talon: see Talon cusp.

4.12 | Leung cusp

4.12.1 | Definition

An additional cusp located in the middle of the occlusal surface. Objective.

4.12.2 | Comments

A Leung cusp is present on premolars only. In X-rays examination, a pulp extension may be seen inside the cusp.

Synonym: Dens evaginatus
Mulberry molar: see Cusps, supernumerary.

4.13 | Tooth, natal

4.13.1 | Definition

A tooth present at birth or erupting within the first month of life (Figure 14). Objective.

4.13.2 | Comments

A tooth erupting between the second and fourth month is called a neonatal tooth. A natal tooth is uncommon, the prevalence at birth is 1/2000 to 1/3500 birth. In 85%, the erupted tooth is the deciduous lower incisors, and in 5%, it concerns upper incisors or molars, and in 10%, it involves supernumerary teeth (Mhaske et al., 2013). Natal teeth are particularly common among some native (First Nation) groups of North America (Carey et al., 2009). Natal teeth are usually mobile and lack root formation.

4.14 | Microdontia

4.14.1 | Definition

Mesiodistal tooth diameter (width) more than 2 SD below mean. Objective.

OR apparently decreased maximum width of tooth (Figure 15). Subjective.
4.14.2 | Comments

Standard references for means and standard deviations by gender are available (Figure 4) (Black, 1890; Lavelle, 1972). Microdontia may affect a single tooth or the entire dentition, which is indicated as localized or generalized microdontia. The most common tooth involved is the lateral incisor. Microdontia goes often along with hypodontia and oligodontia, which should then be assessed and scored separately. Microdontia is typically genetically determined but environmental factors may be also implicated (Jeong, Kim, Song, Sung, & Kim, 2015).

Replaces term: Microdont; Tooth hypoplasia; Tooth hypotrophy

Synonym: Tooth, small; Tooth, underdeveloped

4.15 | Macrodontia

4.15.1 | Definition

Mesiodistal tooth diameter (width) more than 2 SD above mean. Objective.

4.15.2 | Comments

The standard reference for means and standard deviations by gender is available (Figure 4) (Black, 1890; Lavelle, 1972). Macrodontia is uncommon, may affect a single or multiple teeth, and is rarely present in all teeth. A large tooth may also result from fusion of two teeth (Double teeth).

Replaces term: Megadont; Macrodont; Tooth hyperplasia; Tooth hypertrophy

Synonym: Tooth, large; Megalodontia; Globodontia

Tooth, large: see Macrodontia.

Megalodontia: see Macrodontia.

4.16 | Tooth, conical

4.16.1 | Definition

A tooth with a sharply pointed crown or incisal edge (Figure 17). Subjective.
4.16.2 | Comments

A conical shape of a tooth occurs in incisors and canines only. Conical teeth may occur isolated or associated with other dental anomalies, such as hypodontia and oligodontia (Tallon-Walton et al., 2010); this should be assessed and coded separately.

Replaces term: Pointed teeth
Synonym: Conoid teeth
Tooth, conoid: see Tooth, conical.

4.17 | Tooth, barrel-shaped

4.17.1 | Definition

A tooth crown with convex mesial and distal surfaces (Figure 18). Subjective.

4.17.2 | Comments

A barrel shape of a tooth occurs in incisors and canines only. The incisal edge is not pointed. Barrel-shaped teeth are frequently observed in association with hypodontia and oligodontia (Kantaputra, Kaewgahya, Jotikasthira, & Kantaputra, 2014); this should be assessed and coded separately.

4.18 | Tooth, bulbous

4.18.1 | Definition

A tooth crown with a marked cervical area constriction. Subjective.

4.18.2 | Comments

It is mostly seen in molars (Figure 19). The diagnosis bulbous crown needs to be confirmed by X-rays.

4.19 | Tooth, peg-shaped

4.19.1 | Definition

A tooth crown with its mesial and distal sides converging or tapering toward the incisal edge causing severe reduction of mesiodistal diameter (Figure 20). Subjective.
4.19.2 | Comments

A peg shape appearance of a tooth occurs in lateral incisors only (Bot & Salmon, 1977). A peg-shaped tooth is a **microdont** tooth and may occur isolated or associated with other dental anomalies, such as **hypodontia** and **oligodontia** (Reston et al., 2014; Tallon-Walton et al., 2014); this should be assessed and coded separately.

4.20 | Tooth, shovel

4.20.1 | Definition

A tooth with a crown with marked lingual or palatal marginal ridges causing scooped lingual or palatal surfaces (Figure 21). **Subjective**.

4.20.2 | Comments

A shovel shape typically occurs in central upper incisors. Shovel-shaped teeth may occur isolated or associated with other dental anomalies.

4.21 | Tooth, tapered

4.21.1 | Definition

A tooth with a crown that narrows from proximal toward the incisal edge (Figure 22). **Subjective**.

4.21.2 | Comments

Tapering of teeth typically involves incisors (Axelsson, 2005).

**Synonym:** Tooth, screwdriver-shaped

4.22 | Talon cusp

4.22.1 | Definition

A supernumerary cusp on the palatal or lingual side of the maxillary and mandibular anterior teeth (Figure 23). **Subjective**.

4.22.2 | Comments

A talon cusp is found in 1% to 6% of the general population with a large difference in incidence depending on ethnicity. It is uncertain whether it arises as an extra cusp or also as an overdevelopment of an existing cusp. It is rare in the deciduous dentition. A talon cusp extends at least half the distance from the cement–enamel junction to the incisal edge in the palatal or labial surface. It contains enamel, dentin and/or pulp (Kasat, Singh, Saluja, & Ladda, 2014; Mal-lineni, Panampally, Chen, & Tian, 2014).

**Replaces term:** Eagle talon; Dens evaginatus; Cingulum, prominent

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**Figure 23** Talon cusps on both central incisor and invagination at the cingulum site on lateral incisors [Color figure can be viewed at wileyonlinelibrary.com]

**Figure 24** Double teeth in the deciduous dentition. Teeth fused: Fusion of the central incisor with the lateral incisor. Radiograph exhibit the absence of the lateral incisor. Teeth gemination: Tooth germination of right maxillary incisor—clinical aspect and radiograph. Gemination concerned the crown and the beginning of the root. The lateral incisor is present, so the patient has a normal number of teeth [Color figure can be viewed at wileyonlinelibrary.com]
4.23 | Teeth, double

4.23.1 | Definition

Fusion of two adjacent teeth (Figure 24). Objective.

4.23.2 | Comments

The fusion can be complete or be limited to the crown or the root. Typically, incisors and canines form double teeth. Double teeth are more common in the deciduous dentition (0.14–3%) and rare in the permanent dentition (0.2%). Double teeth encompasses fusion, concrescence, and gemination of teeth, which some authors describe with the "twinning" (Hunasgi, Koneru, Manvikar, Vanishree, & Amrutha, 2017). The fusion involves two adjacent, normal teeth. Seemingly, the patient misses a tooth. Concrescence is a condition where the roots are joined only by cementum. The gemination appears when two teeth are developing from one tooth bud leading to a supernumerary tooth formation fused with the normal tooth germ. The patient has a normal number of teeth.

**Replaces term:** Twinning tooth

**Synonym:** Teeth gemination; Teeth fused

Teeth, fused: see Teeth, double.

Teeth, gemination: see Teeth, double.

4.24 | Dens in dente

4.24.1 | Definition

Invagination of part of the crown of a tooth inside the crown (Figure 25). Subjective.

4.24.2 | Comments

Dens in dente results from an invagination of the enamel organ into the dental papilla, extending into the root before initiation of mineralization. The incidence varies from 0.25 to 10% (Hulsmann, 1997). The permanent maxillary lateral incisors are the most frequently involved teeth (6–10% of affected teeth), but it can occur in any tooth type. It occurs more frequently in the permanent dentition and in maxillary teeth. The diagnosis dens in dente needs to be confirmed by X-rays.

**Synonym:** Dens invaginatus

4.25 | Tooth, notched

4.25.1 | Definition

A tooth with a notch of the incisal edge (Figure 26). Subjective.
4.25.2 | Comments
This notch may indicate a *double tooth* formation. A notched tooth should not be confused with *mamelons*.

4.26 | Tooth, semi-lunar
4.26.1 | Definition
An incisor with a half-moon shape incisal edge (Figure 27). *Subjective.*

4.26.2 | Comments
If a notch occupies most of incisal edge, it has been indicated as semi-lunar teeth or crescent-shaped.

*Synonym:* Tooth, crescent-shape; Tooth, semi-circular; Hutchinson incisor

4.27 | Root, anomaly
4.27.1 | Definition
Alteration of the number, shape or the size of roots. *Objective.*

4.27.2 | Comments
Size of roots encompasses their thickness and length. A root may be abnormally short or long.

*Replaces term:* Root dystrophy; Root dysplasia

4.28 | Radiculomegaly
4.28.1 | Definition
Tooth root length more than 2 SD above mean. *Objective.*

*OR* apparently increased tooth root length 5 (Figure 28). *Subjective.*

4.28.2 | Comments
Standard references for means and standard deviations by gender are available (Black, 1890; Lavelle, 1972). It may concern one or multiple teeth. The diagnosis of short roots needs to be confirmed by X-rays.

*Replaces term:* Root dwarfism; root hypoplasia; root hypotrophy

*Synonym:* Rhizomicry; Root, underdeveloped

Root, underdeveloped: see *Root, short.*

4.29 | Root, short
4.29.1 | Definition
Tooth root length more than 2 SD below mean. *Objective.*

*OR* apparently decreased tooth root length (Figure 29). *Subjective.*

4.30 | Molar incisor malformation
4.30.1 | Definition
This is a bundled term as molar incisor malfomation (MIM) and is composed of normal crown with marked cervical constriction, thin, narrow short roots which is a combination of signs that occurs in deciduous and permanent molars. Each of these signs should be assessed and scored separately. *Subjective.*

4.30.2 | Comments
MIM affects one or more roots of deciduous second molars and permanent first molars (Figure 30) (Brusevold, Bie, Baumgartner, Das, &
Espelid, 2017; McCreedy, Robbins, Newell, & Mallya, 2016). Permanent maxillary central incisors may also be affected. The diagnosis requires clinical and radiographic examinations.

4.31 | Taurodontia

4.31.1 | Definition

A crown body–root ratio equal or larger than 1:1. Objective.

Or elongated pulp chambers and apical displacement of the bifurcation or trifurcation of the roots (Figure 31). Subjective.

4.31.2 | Comments

Taurodontia causes a molar shape that is visible on radiographs. Taurodontic teeth display proportionately short roots and enlarged pulp chambers. Normal values for crown body–root ratio are available (Seow & Lai, 1989).

4.32 | Odontodysplasia

4.32.1 | Definition

A tooth with enamel and dentin hypomineralization anomalies causing marked reduction in radio-opacity (Figure 32). Subjective.

4.32.2 | Comments

The diagnosis odontodysplasia requires clinical and radiological exams, in which unusually large pulp chambers and large pulp room chambers with thin enamel and dentin are visible. It may affect either a single tooth or several teeth. The term regional odontodysplasia is used if several teeth are affected. It affects the deciduous and permanent dentitions in the maxilla, the mandible or both, although the maxilla is more frequently involved.

Espelid, 2017; McCreedy, Robbins, Newell, & Mallya, 2016). Permanent maxillary central incisors may also be affected. The diagnosis requires clinical and radiographic examinations.

DE LA DURE-MOLLA ET AL. 1967

FIGURE 30  Molar-incisor-malformation: first permanent molar with short, thin root or rootless teeth [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 31  Taurodontic molars

FIGURE 32  Regional odontodysplasia in the upper right quadrant

FIGURE 33  Extrinsic coloration on the surface of permanent incisors [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 34  Dentin dysplasia [Color figure can be viewed at wileyonlinelibrary.com]
4.33 | Anomaly, dental structure

4.33.1 | Definition

Anomaly in the structure of mineralized tissues of a tooth (Figures 34–39). Subjective.

4.33.2 | Comments

This is a bundled term with which anomalies of enamel and/or dentin and/or cement are indicated. The affected dental structure should be assessed and coded separately.

4.34 | Anomaly, dental color

4.34.1 | Definition

Discoloration of teeth (Figure 33). Subjective.

4.34.2 | Comments

The application of color science within dentistry has permitted the measurement of tooth color in an objective way (Joiner & Luo, 2017). A tooth may show a variety of abnormal colors such as yellow, brown, gray, green color, and red. This should be assessed and added to the
description of a discolored tooth. Discoloration of teeth may be due to extrinsic discoloration (stains that develop on the outer surface of a tooth, Figure 33) or intrinsic discoloration (stains that arise from an endogenous material incorporated into the enamel or dentin and cannot be removed by prophylaxis). It may be also a consequence of dental structure anomaly.

4.35 | Dentin anomaly

4.35.1 | Definition

Structural anomaly of dentin at macroscopic or microscopic level (Figures 34 and 35). Subjective.

4.35.2 | Comments

Dentin anomalies are known only to occur in genetically determined disorders. The structure of dentin is very similar to that of bone, and skeletal dysplasia frequently shows dentin anomalies as well.

Replaces term: Dentin dysplasia; Dentin dystrophy; Dentinogenesis imperfecta

Synonym: Dentin defect

Dentin defect: see Dentin anomaly.

4.36 | Dentin dysplasia

4.36.1 | Definition

This is a bundled term as dentin dysplasia is composed of short roots with pointed ends and taurodontism and intrapulpal calcifications (Figure 34). Subjective.

4.36.2 | Comments

This term designates a genetic condition, and an Element of Morphology rendering its utilization sometimes confusing. The condition is characterized by multiple dental anomalies that affect both deciduous and permanent dentitions. It can exist in isolation or be associated with other signs and symptoms of various syndromes.

4.37 | Dentinogenesis imperfecta

4.37.1 | Definition

This is a bundled term as dentinogenesis imperfecta and is composed of crown discoloration, bulbous crown, short roots, intra-pulpal calcification, which is a combination of signs that occurs in several disorders in deciduous and permanent teeth. Each of these signs should be assessed and scored separately (Figure 35).

4.37.2 | Comments

This term designates a genetic condition, and an Element of Morphology rendering its utilization sometimes confusing. The condition is characterized by multiple dental anomalies that affect both deciduous and permanent dentitions. It can exist in isolation or be associated with other signs and symptoms of various syndromes. Dentinogenesis imperfecta shows variable expression with mild, moderate, and severe forms that correspond respectively to earlier dentin dysplasia type II, dentinogenesis imperfecta type II, and dentinogenesis imperfecta type III of the Shield classification, allelic to dentine sialophosphoprotein defects (de La Dure-Molla et al., 2015).

4.38 | Enamel dysplasia

4.38.1 | Definition

Alteration of color, shape, surface, and/or structure of enamel (Figures 36–40). Subjective.

4.38.2 | Comments

Enamel dysplasia may reflect qualitative or quantitative alteration of enamel structure. Enamel dysplasia encompasses enamel hypoplasia, enamel agenesis, enamel hypomineralization, enamel hypomaturation, and amelogenesis imperfecta.

Synonym: Enamel anomaly; Enamel defect
4.39 | Enamel, hypoplasia

4.39.1 | Definition

A quantitative defect in enamel formation (Figure 36). Subjective.

4.39.2 | Comments

Enamel hypoplasia can be caused by genetic or environmental factors. It may occur in both deciduous and permanent dentitions, although more often in the permanent dentition. Enamel hypoplasia may concern a single tooth, several teeth, or the complete dentition and may affect part or the complete surface of the tooth. Enamel hypoplasia regroups different clinical aspects: localized hypoplasia, generalized hypoplasia, enamel pits, enamel striae, and grooves defects. The term should be used to describe a quantitative defect of enamel. Enamel hypotrophy cannot be used as hypotrophy indicates loss of cells, whereas enamel is an acellular structure and thus not a tissue.

Replaces term: enamel hypotrophy

Synonym: Enamel, thin; Enamel, pitted; Enamel, underdeveloped

4.40 | Enamel, agenesis

4.40.1 | Definition

Complete or almost complete absence of enamel (Figure 37). Subjective.

4.40.2 | Comments

Enamel agenesis can indicate a total absence of enamel or the presence of a very thin enamel layer that is difficult to visualize during clinical examination. It may need microscopic studies to determine whether any enamel is still present. It can be present isolated and as part of rare syndromic entities (de La Dure-Molla et al., 2015; Huckert et al., 2015).

Enamel hypoplasia: see Enamel, hypomineralization.

4.41 | Enamel, hypomineralization

4.41.1 | Definition

Enamel with a brown discoloration and brittle aspect. (Figure 38). Subjective.

4.41.2 | Comments

Enamel hypomineralization can be caused by genetic or environmental factors. It may occur in both deciduous and permanent dentitions, although more often in the permanent dentition. It may concern a single tooth, several teeth, or the complete dentition and may affect part or the complete surface of the tooth. Enamel hypomineralization is a qualitative defect of enamel, in which the enamel can be rough and softer. Affected teeth may be sensitive. Enamel hypomineralization can be part of molar incisor hypomineralization (hypomineralisation of systemic origin of one to four permanent first molars, frequently associated with affected incisors) (Weerheijm, 2003) and of hypomineralized second primary molars (or deciduous molar hypomineralisation, which indicates idiopathic hypomineralization of one to four second deciduous molars) (Negre-Barber, Montiel-Company, Boronat-Catala, Catala-Pizarro, & Almerich-Silla, 2016).

Synonym: Enamel, hypocalcification

4.42 | Enamel, hypomature

4.42.1 | Definition

Enamel with a white or brown discoloration without hypoplasia (Figure 39). Subjective.

4.42.2 | Comments

Enamel maturation is a process through which enamel matrix proteins are removed to allow full growth of the enamel hydroxyapatite crystals. Hypomature enamel can be caused by genetic or environmental factors. It may occur in both deciduous and permanent dentitions, although more often in the permanent dentition. Hypomature enamel may concern a single tooth, several teeth, or the complete dentition and may affect part or the complete surface of the tooth. The enamel is usually hard, colored but not translucid. It is a qualitative defect of enamel.

Synonym: Enamel opacity

Enamel opacity: see Enamel, hypomature.

Enamel, pitted: see Enamel hypoplasia.

Enamel, thin: see Enamel hypoplasia.

Enamel underdevelopment: see Enamel hypoplasia.

4.43 | Amelogenesis imperfecta

4.43.1 | Definition

This is a bundled term as amelogenesis imperfecta and is composed of crown discoloration and/or enamel dysplasia (Figure 40). Subjective.

FIGURE 41 Cementum hyperplasia at the root of the mandibular left second premolar
Amelogenesis imperfecta generally affects all elements and both deciduous and permanent teeth. The term designates both a genetic condition, and an Element of Morphology rending its utilization sometimes confusing. It describes enamel defects (hypoplasia, hypomineralization, hypomaturation) that usually affect (but not always) both deciduous and permanent dentitions.

4.44 | Cementum, hypoplasia

4.44.1 | Definition

The decrease or absence of cementum. Subjective.

4.44.2 | Comments

The cementum anchors the periodontal ligament attachment fiber between the tooth root and the alveolar bone. Its absence leads to early loss of teeth.

Replaces term: Cementum aplasia

FIGURE 42 | Pulp calcification within the pulp chamber of the molar and the second premolar

FIGURE 43 | Pulp obliteration in dentinogenesis imperfecta

Cementum, overdeveloped: see Cementum, overgrowth.

4.45 | Cementum, overgrowth

4.45.1 | Definition

Excess of cementum on the tooth root surface (Figure 41). Subjective.

4.45.2 | Comments

The excessive buildup of normal cementum (calcified tissue) on the roots of one or more teeth is an idiopathic, non-neoplastic condition. Cementum overgrowth may be either hyperplasia or hypertrophy of the cement; these terms can only be used if histological evidence of hypertrophy or hyperplasia have been established.

Replaces term: Cementation hyperplasia; Cementum hypertrophy; Drumstick-shaped root

Synonym: Hypercementosis; Cementum, overdeveloped

Hypercementosis: see Cementum, overgrowth.

4.46 | Pulp, calcification

4.46.1 | Definition

Calcifications of dental pulp (Figure 42). Subjective.
4.46.2 | Comments

Calcifications may appear as punctate calcifications, irregular, roughly spherical mineralized masses in any part of the pulp. It may occur isolated or associated to calcifications elsewhere such as the carotid arteries and kidneys (Yeluri, Kumar, & Raghav, 2015). The diagnosis pulp calcifications can be established using radiological studies.

Replaces term: Pulpoliths

Synonym: Pulp stones; Pulp denticles
Pulp denticles: see Pulp, calcification.
Pulp, flame-shaped: see Pulp, Thistle tube shaped.

4.47 | Pulp, obliteration

4.47.1 | Definition

Mineralized substance filling the entire dental pulp space (Figure 43). Subjective.

4.47.2 | Comments

The diagnosis pulp obliteration can be established using radiological studies. Gradual obliteration of the pulp is a physiologic process that occurs with aging. On radiographs the contours of the pulp disappear in part or totally, but histologically pulpal tissue remains present.

Pulp stones: see Pulp, calcification.

4.48 | Pulp, thistle tube shaped

4.48.1 | Definition

A thistle tube shape of the pulp chamber (Figure 44). Subjective.

4.48.2 | Comments

Enlarged coronal pulp chamber with narrow pulp canals giving a radiographic appearance of the shape of a thistle tube or a flame. It may occur isolated or associated to other dental anomalies rare diseases such as dentinogenesis imperfecta, which should be assessed and coded separately. The diagnosis thistle tube shape pulp requires clinical and radiographic examinations.

Synonym: Pulp, flame-shaped
Eruption, advanced: see Tooth, premature eruption.

4.49 | Eruption, delayed

4.49.1 | Definition

Eruption of a tooth more than 2 SD beyond the mean eruption age (Figure 45). Objective.

4.49.2 | Comments

Eruption is defined by the appearance of a tooth that has pierced the oral mucosa. There are established norms for the timing of eruption in both deciduous and permanent teeth (Lunt & Law, 1974; McDonald et al., 2004). Eruption delay may affect either the deciduous teeth, permanent teeth, or both. The absence of shedding of deciduous teeth may be seen in association with delayed permanent tooth eruption or agenesis of successional permanent teeth. The diagnosis eruption delayed requires clinical and radiographic examinations.

4.50 | Eruption, failure

4.50.1 | Definition

A tooth which does not erupt within the teeth eruption timeline and after the loss of eruption potential (Figure 46). Objective.

4.50.2 | Comments

Usually a tooth erupts at a stage of half or two/third root formation. There are established norms for the timing of eruption and tooth stages in both deciduous and permanent teeth (Lunt & Law, 1974; McDonald et al., 2004) It may be difficult to discern Delayed eruption from failure of eruption: failure indicates it will never erupt, delayed indicates it may still erupt. Eruption failure may be caused by an isolated obstacle (supernumerary teeth), ankylosis of impacted teeth, or disturbances of biological eruption pathway. Partial or complete non-eruption of not initially ankylosed teeth due to a disturbed eruption mechanism result in a severe form of posterior open bite that usually worsens from anterior to posterior. Eruption failure is usually asymmetrical, affects more posterior teeth and both dentition may be involved (Pilz et al., 2014). The diagnosis eruption failure requires clinical and radiographic examinations.

Synonym: Tooth, impacted; Tooth, retained

4.51 | Primary failure of eruption

4.51.1 | Definition

Eruption failure of permanent teeth in the absence of an obstacle hindering tooth progression toward the oral cavity. Objective.

FIGURE 46 Eruption, failure of all permanent molars
4.51.2 | Comments

This is a bundled term as Primary failure of eruption (PFE) and is composed of eruption failure, tooth ankylosis, tooth infraoccluded, posterior lateral open bite. Each of these signs should be assessed and scored separately. The term designates both a genetic condition, and an Element of Morphology rending its utilization sometimes confusing.

The non-eruption mechanism defect is due to an abnormal dental follicle, partially or totally blocking tooth progression. It usually involves one or multiple molar sectors. Incisors, canines, and premolars may also be involved but with a reduced individual frequency. The diagnosis Primary failure of eruption failure requires clinical and radiographic examinations.

Tooth, impacted: see Eruption, failure.

4.52 | Tooth, premature loss

4.52.1 | Definition

Exfoliation of a tooth more than 2 SD earlier than the normal age for the deciduous teeth. Exfoliation of a permanent tooth is per se abnormal. (Figure 47). Objective.

4.52.2 | Comments

Premature loss of a tooth may concern deciduous and permanent teeth. The range of ages in years for normal exfoliation of deciduous teeth usually precedes the mean age of eruption of each tooth by a year or less (Hennekam et al., 2010; Kleigman, Behrman, Jenson, & Stanton, 2007).

Replaces term: Exfoliation, early

4.53 | Tooth, premature eruption

4.53.1 | Definition

A tooth which erupts more than 2 SD earlier than the mean eruption age (Figure 48). Objective.

4.53.2 | Comments

Eruption is defined by the appearance of a tooth that has pierced the oral mucosa. There are established norms for the timing of eruption of both deciduous and permanent teeth (Lunt & Law, 1974; McDonald et al., 2004) Tooth eruption sequences follow broadly similar and symmetrical patterns during establishment of the deciduous and permanent dentitions, although wide individual variation in timing is common. Eruption timing depends on the population studied. Norms are typically specific for populations (Baylis & B. R., 2017; Verma et al., 2017).

Synonym: Eruption advanced; Tooth, advanced development

4.54 | Tooth, infraoccluded

4.54.1 | Definition

A tooth with its occlusal surface at a lower level than the adjacent teeth (Figure 49). Subjective.

4.54.2 | Comments

Infraocclusion of a tooth typically concerns deciduous molars. Two anomalies may be described: (1) a halt of the eruption of a tooth shortly after emergence in the oral cavity, despite the lack of a physical obstacle in the eruption pathway (Nielsen, Becktor, & Kjaer, 2006);
4.55 | Tooth, ankylosis

4.55.1 | Definition

Fusion of a tooth with alveolar bone (Figure 50). Subjective.

4.55.2 | Comments

Ankylosis is uncommon in the deciduous dentition and very rare in the permanent dentition. It may be observed after trauma. Ankylosis may occur at the crown or root level.

4.56 | Teeth, malposition

4.56.1 | Definition

Location of a tooth out of its normal position or orientation (Figure 51). Subjective.

4.56.2 | Comments

Anomalies of tooth position can be classified into ectopic (in an abnormal location), transmigration (pre-eruptive migration to a location some distance away), transposition (positional interchange of two adjacent teeth), rotation (tooth turning along its long axis), crowding (malalignment of tooth row). This should be added in describing a malpositioned tooth.

Replaces term: Irregular dentition

4.57 | Dental crowding

4.57.1 | Definition

Changes in alignment of teeth in the dental arch (Figure 54). Subjective.
4.57.2 | Comments

There is a discrepancy in the space needed to align the teeth and the size of the alveolar ridge.

- Replaces term: Irregular teeth, Irregular dentition
- Synonym: Teeth, malalignment; Teeth, misalignment

Teeth, malalignment: see Dental crowding.
Teeth, misalignment: see Dental crowding.

4.58 | Teeth, spaced

4.58.1 | Definition

Separation of teeth of the same dental arch by wider spaces than normal (Figure 52). Subjective.

4.58.2 | Comments

Wide spacing can be secondary to increased room by an unusually large dental arch or smaller teeth (microdontia) or if mixed deciduous and secondary dentition are present. Slight spacing between the deciduous teeth is physiological, and experience in evaluation is important in determining this feature. This descriptor must be distinguished from a diastema. The difference between diastema and widely spaced teeth is that diastema is between two teeth and widely spaced teeth between more than two teeth. Normal values of dental spacing are not available.

- Replaces term: Diastemata
- Dental malocclusion: see Occlusion, anomaly.

4.59 | Diastema

4.59.1 | Definition

Increased space between two adjacent teeth (Figure 53). Subjective.

4.59.2 | Comments

Usually, there is a contact surface between the lateral sides of two adjacent teeth, at their broadest contour area. A diastema can apply to any pair of teeth. The term should be modified by a descriptor of the involved teeth. This descriptor must be distinguished from widely spaced teeth. Midline diastema refers to the diastema between the upper central incisors.

4.60 | Occlusion anomaly

4.60.1 | Definition

Alteration of the dental arch relationships in form or position (Figure 55). Objective.

4.60.2 | Comments

Occlusion anomalies include a large variety of disturbed occlusion such as disto-occlusion, mesio-occlusion, midline deviation of dental arch, overjet, and posterior lingual occlusion of mandibular teeth. The Angle classification is used to define dental relationship using the first permanent maxillary molar position as a reference: Class I: normocclusion, Class II (distooclusion) retrognathism; Class III mesiocclusion (prognathism) (Angle, 1899).

- Synonym: Dental malocclusion

4.61 | Open bite

4.61.1 | Definition

Visible anterior space between the dental arches in occlusion (Figure 56). Subjective.
4.61.2 | Comments

Open bite produces an absence of vertical overlap of the two dental arches. It may be associated with malocclusion, but this should be assessed and coded separately. Open bite may occur in the anterior or posterior part of the arches which are called anterior open bite, frontal open bite and lateral open bite, respectively. This should be added in describing an open bite.

4.62 | Cross bite

4.62.1 | Definition

Lingual occlusion of buccal cusps and/or incisal edge of maxillary teeth to the buccal cusps and/or incisal edge of mandibular teeth (Figure 57). Subjective.

4.62.2 | Comments

Cross bite may occur unilaterally, bilaterally, or frontally. A total cross bite with buccal displacement of the maxillary posterior teeth, with or without contact between the lingual surface of the maxillary lingual cusp and the buccal surface of the buccal cusp of its mandibular antagonist, has been called scissors bite. If only a single tooth is affected, the term single cross bite can be used.

4.63 | Overbite, increased

4.63.1 | Definition

Vertical overlap (frontal plane) of maxillary incisors over mandibular incisors exceeding 2 mm (Figure 58). Objective.

4.63.2 | Comments

An overjet concerns only anterior teeth. Supraocclusion: see Overbite, increased. An overbite concerns only anterior teeth. Synonym: Supraocclusion; Deep bite

4.64 | Overjet, increased

4.64.1 | Definition

Horizontal overlap (sagittal plane) of upper frontal teeth over the lower frontal teeth exceeding 3.5 mm (Figure 59). Objective.

**FIGURE 56** Open bite evident in the absence of contact between dental arches [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 57** Cross bite (anterior and lateral) [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 58** Overbite, increased evident in overlap of maxillary incisors over the mandibular ones [Color figure can be viewed at wileyonlinelibrary.com]
4.65 | Gingival, overgrowth

4.65.1 | Definition

Thickening of the gingiva (Figure 60). Subjective.

4.65.2 | Comments

The degree of thickening ranges from involvement of only the interdental papillae to gingival overgrowth covering the entire tooth crown. The gingival soft tissue overlying the alveolar ridge thickens. It may occur isolated, associated to orthodontic treatment (Zanatta, Ardenghi, Antoniazzi, Pinto, & Rosing, 2014), systemic treatment (Miranda et al., 2001), and generalized (Jaureguiberry et al., 2012). Gingival overgrowth can also be seen subsequently to external factors (phenytoin; cyclosporin A; nifediprin) or can be genetically determined. Gingival overgrowth can be caused by gingival hypertrophy and gingival hyperplasia, which can only be diagnosed using histological studies.

Replaces term: Gingival hyperplasia; Gingival hypertrophy
Synonym: Gingival overdevelopment; Gingiva, enlarged

FIGURE 59  Overjet increased evident in the increase of horizontal distance between maxillary and mandibular teeth [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 60  Gingival overgrowth [Color figure can be viewed at wileyonlinelibrary.com]

5 | NOSOLOGY OF GENETICALLY DETERMINED DENTAL DISORDERS

The presently proposed nosology of genetically determined dental disorders consists of 408 entities (Table 1). Dental non-developmental anomalies registered in OMIM, which are at least in part acquired, such as dental caries, are not included. Disorders going along with malocclusion of which the origin can be completely acquired to completely genetically determined, and which can be dental but also non-dental, are also excluded. Some disorders pertaining to a group are included, whereas other are not. For example, within the group of epidermolysis bullosa disorders, the dystrophica type is not included as its only associated dental sign is caries, but the junctional type is included as it goes along with enamel anomalies.

Each of the eight dental anomaly groups is subdivided into isolated and syndromic forms. Syndromes are grouped according to the recommendations for the grouping of rare disorders established by the European Reference Networks (Evangelista et al., 2016). Some syndromes go along with several different dental anomalies, such as Johanson-Blizzard syndrome with dental agenesis and severe microdontia. These disorders are classified in only one group, and other main dental phenotypes are added in the “notes” column. In 322 of the 408 disorders (79%), a gene is identified. In an additional 17 (4%), a candidate locus is known. The efforts made in establishing a common characterization of dental and craniofacial disorders, both isolated and syndromic, as well as in ascertaining their developmental and genetic common traits (for review: Bloch-Zupan et al., 2012; Klein et al., 2013; Mitsiadis & Luder, 2011; Thesleff, 2014) are contributing to these high percentages. However, this percentage could not be linked to the genetic diagnostic rates in practice. Isolated oro-dental disorders account for 53 of the 408 entities (13%), the remaining 87% are syndromes. In comparing the various dental anomalies, we find that dental agenesis is present in 121 disorders, supernumerary teeth in 18 disorders, dental size and/or shape disorders in 29 disorders, enamel anomalies in 105 disorders, dentin anomalies in 35 disorders, anomalies in dental eruption in 40 disorders, periodontal and gingival anomalies in 52 disorders, and tumor-like anomalies in eight disorders.

The development in sequencing techniques allowing to evaluate for variants in groups of genes causing specific signs or symptoms (NGS panel sequencing) has demonstrated that disorders initially described as occurring isolated could be allelic to syndromes, and vice versa. This is occurring in dental disorders as well. For example, variants in EDA were first described causing ectodermal dysplasia but were subsequently detected in individuals with dental agenesis without other signs of ectodermal dysplasia, and similar widening of phenotypes being caused by variants in single genes have been reported in several other genes such as COL17A1, DLX3, and LAMA3 (Poulter et al., 2014; Prasad et al., 2016; Yang et al., 2013).

We hope that these clinical descriptions are useful in patient’s care, especially in case of multi-disciplinary discussions. Dental anomalies are relevant clinical signs and may provide key clues for
differential diagnosis of rare disorders, and the present nosology may be helpful in this respect as well. The present nosology is the first comprehensive nosology in Dentistry. Undoubtedly, it will need regularly updating. Furthermore, we welcome remarks and criticisms by colleagues around the world to ameliorate both the definitions and the nosology.

D[4]/phenodont: www.phenodont.org

Human Phenotype Ontology: www.human-phenotype-ontology.org

ICD10-ICD11 MMS: Revised International Classification of Disorders for Mortality and https://icd.who.int/dev11/l-m/en

OMIM (Online Mendelian Inheritance in Man): http://www.ncbi.nlm.nih.gov/omim/

Orphanet: www.orpha.net (Rath et al., 2012).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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