Nosology and Classification of Genetic Skeletal Disorders: 2010 Revision

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Genetic disorders involving the skeletal system arise through disturbances in the complex processes of skeletal development, growth and homeostasis and remain a diagnostic challenge because of their variety. The Nosology and Classification of Genetic Skeletal Disorders provides an overview of recognized diagnostic entities and groups them by clinical and radiographic features and molecular pathogenesis. The aim is to provide the Genetics, Pediatrics and Radiology community with a list of recognized genetic skeletal disorders that can be of help in the diagnosis of individual cases, in the delineation of novel disorders, and in building bridges between clinicians and scientists interested in skeletal biology. In the 2010 revision, 456 conditions were included and placed in 40 groups defined by molecular, biochemical, and/or radiographic criteria. Of these conditions, 316 were associated with mutations in one or more of 226 different genes, ranging from common, recurrent mutations to “private” found in single families or individuals. Thus, the Nosology is a hybrid between a list of clinically defined

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of genes, proteins and pathways involved in skeletal biology. The Nosology should be useful for the diagnosis of patients with genetic skeletal diseases, particularly in view of the information flood expected with the novel sequencing technologies; in the delineation of clinical entities and novel disorders, by providing an overview of established nosologic entities; and for scientists looking for the clinical correlates of genes, proteins and pathways involved in skeletal biology.

Key words: skeletal genetics; osteochondrodysplasias; nosology; dysostoses; molecular basis of disease

INTRODUCTION

In the 1960s, accumulating evidence that genetic skeletal disorders were clinically and genetically heterogeneous prompted a group of international experts to prepare a document to reach an agreement on the nomenclature of what was then called “constitutional (or intrinsic) disorders of bone” [1970, 1971a,b,c,d; McKusick and Scott, 1971]. The “Nomenclature” was meant to bring together experts in radiology, clinical genetics, and pediatrics to agree on the denomination and classification of skeletal disorders, syndromes and metabolic diseases that were being newly described. Revisions have been prepared in 1977, 1983, 1992, and 1997 [1978, 1979, 1983, 1998, Rimoin, 1979; Spranger, 1992; Lachman, 1998]. Following the establishment of the International Skeletal Dysplasia Society (ISDS) in 1999, and to cope with the increasing complexity of information, revisions of the Nosology have been delegated to an expert group nominated ad hoc within the ISDS to ensure an adequate representation of clinical, radiological and molecular expertise (2001 and 2006 revisions) [Hall, 2002; Superti-Furga and Unger, 2007].

METHODS

The Nosology Group of the International Skeletal Dysplasia Society met in August 2009. A consensus was reached for changes to be made to the grouping of disorders and about the inclusion of individual disorders. The drafts were circulated after the meeting and an effort was made to monitor recent publications up to November 2010. The criteria used for inclusion of individual disorders were unchanged from the previous revision. They were:

1. Significant skeletal involvement, corresponding to the definition of skeletal dysplasias, metabolic bone disorders, dysostoses, and skeletal malformation and/or reduction syndromes.
2. Publication and/or listing in MIM (meaning that observations should not find their way into the Nosology before they achieve peer-reviewed publication status).
3. Genetic basis proven by pedigree or very likely based on homogeneity of phenotype in unrelated families.
4. Nosologic autonomy confirmed by molecular or linkage analysis and/or by the presence of distinctive diagnostic features and of observation in multiple individuals or families.

RESULTS

Four hundred fifty-six different conditions were included and placed in 40 groups defined by molecular, biochemical and/or radiographic criteria. Of these conditions, 316 (2006 revision: 215) were associated with one or more of 226 (2006 revision: 140) different genes. The results are presented in Table I. Within a group, disorders with known molecular basis have been listed preceding those with lesser degree of evidence; however, variants of the same disorder have been kept together.

The organization of groups has been further changed in comparison to the 2006 version. Two new groups based on a common affected molecule or biochemical pathway have been created (TRPV4 group and Aggrecan group). The TRPV4 group includes disorders that are relatively common and that constitute a new prototypic spectrum ranging from mild to lethal. Aggrecan is one of the important structural molecules in cartilage and it would not be surprising if more disorders would find their way into this group in the future. Thus, groups 1–8 are based on a common underlying gene or pathway.

Groups 9–17 are based on the localization of radiographic changes to specific bone structures (vertebrae, epiphyses, metaphyses, diaphysis, or combination thereof) or of the involved segment (rhizo, meso, oracro). Groups 18–20 are defined by macroscopic criteria in combination with clinical features (bent bones, slender bones, presence of multiple dislocations). Groups 21–25 and 28 take into account features of mineralization (increased or reduced bone density, impaired mineralization, stippling, osteolysis). Group 27 encompasses the large group of lysosomal disorders with skeletal involvement. Group 29 comprises disorders with so-called abnormal (previously “anarchic”) development of skeletal components such as exostoses, enchondromas, and ectopic calcification. It is particularly heterogeneous and may need to be revised in the future with the help of newer molecular data.

Group 23, comprising the osteopetrosis (OP) variants and related disorders, has been expanded following the identification of distinct genetic defects in various variants of osteopetrosis. The diversity of molecular mechanisms involved and the presence of clinical, biochemical and/or histologic features that distinguish between the various OP forms justify the subdivision of the “OP phenotype” in the many subtypes.

Group 25 (Osteogenesis Imperfecta and decreased bone density group) has had special attention. The Silence classification, published 30 years ago, provided a first systematic clinical classification and made correlations to the inheritance pattern of individual clinical types [Silence and Rimoin, 1978; Silence et al., 1979a,b]. Today, a surprising genetic complexity of the molecular bases ofOI has been revealed, and at the same time the extensive phenotypic variation arising from single loci has been documented clearly. It seemed therefore untenable to try and maintain tight correlations between “Silence types” and their molecular basis. It was agreed upon to retain the Silence classification as the prototypic and universally accepted way to classify the degree of severity in OI; and to free the Silence classification from any direct molecular reference. Thus, the many genes that may cause osteogenesis imperfecta have been listed separately. The proliferation of “OI types” to reflect
| Group/name of disorder                                           | Inheritance | MIM No. | Locus | Gene | Protein | Notes                                                                 |
|-----------------------------------------------------------------|-------------|---------|-------|------|---------|----------------------------------------------------------------------|
| **1. FGFR3 chondrodysplasia group**                              |             |         |       |      |         |                                                                      |
| Thanatophoric dysplasia type 1 (TD1)                             | AD          | 187600  | 4p16.3| FGFR3| FGFR3   | Includes previous San Diego type                                      |
| Thanatophoric dysplasia type 2 (TD2)                             | AD          | 187601  | 4p16.3| FGFR3| FGFR3   |                                                                      |
| Severe achondroplasia with developmental delay and acanthosis  | AD          | See     | 4p16.3| FGFR3| FGFR3   |                                                                      |
| nigricans (SADDAN)                                               | AD          | 187600  |       |      |         |                                                                      |
| Achondroplasia                                                   | AD          | 100800  | 4p16.3| FGFR3| FGFR3   | Inactivating mutation                                                |
| Hypochondroplasia                                                | AD          | 146000  | 4p16.3| FGFR3| FGFR3   |                                                                      |
| Camptodactyly, tall stature, and hearing loss syndrome [CATSHL]  | AD          | 187600  | 4p16.3| FGFR3| FGFR3   |                                                                      |
| Hypochondroplasia-like dysplasia(s)                             | AD, SP      |         |       |      |         |                                                                      |

**2. Type 2 collagen group and similar disorders**

| Group/name of disorder                                           | Inheritance | MIM No. | Locus | Gene | Protein | Notes                                                                 |
|-----------------------------------------------------------------|-------------|---------|-------|------|---------|----------------------------------------------------------------------|
| Achondrogenesis type 2 (ACG2; Langer–Saladin)                   | AD          | 200610  | 12q13.1| COL2A1| Type 2 collagen                                                        |
| Platyspondylic dysplasia, Torrance type                         | AD          | 151210  | 12q13.1| COL2A1| Type 2 collagen                                                        |

**3. Type 11 collagen group**

| Group/name of disorder                                           | Inheritance | MIM No. | Locus | Gene | Protein | Notes                                                                 |
|-----------------------------------------------------------------|-------------|---------|-------|------|---------|----------------------------------------------------------------------|
| Stickler syndrome type 2                                         | AD          | 604841  | 1p21  | COL11A1| Type 11 collagen alpha-1 chain                                       |
| Marshall syndrome                                                | AD          | 154780  | 1p21  | COL11A1| Type 11 collagen alpha-1 chain                                       |
| Fibrochondrogenesis                                              | AR          | 228520  | 1p21  | COL11A1| Type 11 collagen alpha-1 chain                                       |
| Otospondylomegaeiphyseal dysplasia (OSMED), recessive type       | AR          | 215150  | 6p21.3| COL11A2| Type 11 collagen alpha-2 chain                                       |
| Group/name of disorder                                                                 | Inheritance | MIM No.    | Locus       | Gene       | Protein                              | Notes                                                                 |
|---------------------------------------------------------------------------------------|-------------|------------|-------------|------------|--------------------------------------|----------------------------------------------------------------------|
| Otospondyloepiphysial dysplasia (OSMED), dominant type (Weissenbacher–Zweymüller syndrome, Stickler syndrome type 3) | AD          | 215150     | 6p21.3      | COL11A2    | Type 11 collagen alpha-2 chain        | See also Stickler syndrome type 1 in group 2                           |
| 4. Sulfation disorders group                                                           |             |            |             |            |                                      |                                                                      |
| Achondrogenesis type 1B (ACG1B) AR 600972 5q32–33                                    | AR          | 600972     | 5q32–33     | DTDST      | SLC26A2 sulfate transporter           | Formerly known as Fraccaro type achondrogenesis                        |
| Atelosteogenesis type 2 (AO2) AR 256050 5q32–33                                      | AR          | 256050     | 5q32–33     | DTDST      | SLC26A2 sulfate transporter           | Includes de la Chapelle dysplasia, McAlister dysplasia, and “neonatal osseous dysplasia” |
| Diastrophic dysplasia (DTD) MED, autosomal recessive type (rMED, EDM4)                 | AR          | 222600     | 5q32–33     | DTDST      | SLC26A2 sulfate transporter           | See also multiple epiphyseal dysplasias and pseudoachondroplasia group (group 9) |
| SEMD, PAPSS2 type AR 603005 10q23–q24                                               | AR          | 603005     | 10q23–q24   | PAPSS2     | PAPS-Synthetase 2                    | Formerly “Pakistani type.” See also SEMD group (group 11)              |
| Chondrodysplasia with congenital joint dislocations, CHST3 type                      | AR          | 608637     | 10q22.1     | CHST3      | Carbohydrate sulfotransferase 3; chondroitin 6-sulfotransferase | Includes recessive Larsen syndrome, humero-spinal dysostosis, and SED Omani type |
| Ehlers–Danlos syndrome, CHST14 type (“musculo-skeletal variant”)                     | AR          | 601776     | 15q14       | CHST14     | Carbohydrate sulfotransferase 14; dermatan 4-sulfotransferase | Includes Adducted Thumb–Clubfoot syndrome                               |
| See also group 7 and group 26 for other conditions with multiple dislocations         |             |            |             |            |                                      |                                                                      |
| 5. Perlecan group                                                                      |             |            |             |            |                                      |                                                                      |
| Dyssegmental dysplasia, Silverman-Handmaker type                                       | AR          | 224410     | 1q36–34     | PLC (HSPG2)| Perlecan                             |                                                                      |
| Dyssegmental dysplasia, Rolland-Desbuquois type                                       | AR          | 224400     | 1q36–34     | PLC (HSPG2)| Perlecan                             |                                                                      |
| Schwartz–Jampel syndrome (myotonic chondrodystrophy)                                   | AR          | 255800     | 1q36–34     | PLC (HSPG2)| Perlecan                             | Mild and severe forms; includes previous Burton dysplasia             |
| 6. Aggrecan group                                                                      |             |            |             |            |                                      |                                                                      |
| SED, Kimberley type                                                                   | AD          | 608361     | 15q26       | AGC1       | Aggrecan                             |                                                                      |
| SEMD, Aggrecan type                                                                   | AR          | 612813     | 15q26       | AGC1       | Aggrecan                             |                                                                      |
| Familial osteochondritis dissecans                                                     | AD          | 165800     | 15q26       | AGC1       | Aggrecan                             |                                                                      |
| 7. Filamin group and related disorders                                                  |             |            |             |            |                                      |                                                                      |
| Frontometaphyseal dysplasia                                                            | XLD         | 305620     | Xq28        | FLNA       | Filamin A                            | Some cases apparently lack FLNA mutations                             |
| Osteodysplasty Melnick–Needles                                                        | XLD         | 309350     | Xq28        | FLNA       | Filamin A                            |                                                                      |
| Condition                                      | Mode | Chromosome | Gene | Description                                                                 |
|------------------------------------------------|------|------------|------|-----------------------------------------------------------------------------|
| Otopalatodigital syndrome type 1 (OPD1)       | XLD  | Xq28       | FLNA | Filamin A                                                                   |
| Otopalatodigital syndrome type 2 (OPD2)       | XLD  | Xq28       | FLNA | Filamin A                                                                   |
| Terminal osseous dysplasia with pigmentary defects (TODPD) | XLD  | Xq28       | FLNA | Filamin A                                                                   |
| Atelosteogenesis type 1 (AO1)                 | AD   | 3p14.3     | FLNB | Filamin B                                                                   |
| Atelosteogenesis type 3 (AO3)                 | AD   | 3p14.3     | FLNB | Filamin B                                                                   |
| Larsen syndrome (dominant)                    | AD   | 3p14.3     | FLNB | Filamin B                                                                   |
| Spondylo-carpal-tarsal dysplasia              | AD   | 3p14.3     | FLNB | Filamin B                                                                   |
| Spondylo-carpal-tarsal dysplasia              | AR   | 3p14.3     | FLNB | Filamin B                                                                   |
| Franck–ter Haar syndrome                      | AR   | 3p14.3     | FLNB | Filamin B                                                                   |
| Serpentine fibula—polycystic kidney syndrome  | AD?  | 5q35.1     | SH3PD2B | TKS4                                                                      |
| Serpentine fibula—polycystic kidney syndrome  | AD   | 5q35.1     | SH3PD2B | TKS4                                                                      |
| Serpentine fibula—polycystic kidney syndrome  | AD   | 5q35.1     | SH3PD2B | TKS4                                                                      |
| Metatropic dysplasia                          | AD   | 12q24.1    | TRPV4 | Transient receptor potential cation channel, subfamily V, member 4         |
| Metatropic dysplasia                          | AD   | 12q24.1    | TRPV4 | Transient receptor potential cation channel, subfamily V, member 4         |
| Metatropic dysplasia                          | AD   | 12q24.1    | TRPV4 | Transient receptor potential cation channel, subfamily V, member 4         |
| Chondroectodermal dysplasia (Ellis—van Creveld) | AR   | 4p16       | EVC1  | EvC gene 1                                                                  |
| Short rib—polydactyly syndrome (SRPS) type 1/3 [Saldino-Noonan/Verma-Naumoff] | AR   | 4p16       | EVC2  | EvC gene 2                                                                  |
| SRPS type 1/3 [Saldino-Noonan/Verma-Naumoff]  | AR   | 11q22.3    | DYNC2H1 | Dynein, cytoplasmic 2, heavy chain 1                                       |
| SRPS type 1/3 [Saldino-Noonan/Verma-Naumoff]  | AR   | 3q25.33    | IFT80 | Intraflagellar transport 80 (homolog of)                                   |
| SRPS type 2 [Majewski]                        | AR   | 4p16       | EVC1  | EvC gene 2                                                                  |
| SRPS type 2 [Majewski]                        | AR   | 4p16       | EVC1  | EvC gene 2                                                                  |

See also group 4 for recessive Larsen syndrome and group 26 for conditions with multiple dislocations.

8. TRPV4 group

| Condition                                      | Mode | Chromosome | Gene | Description                                                                 |
|------------------------------------------------|------|------------|------|-----------------------------------------------------------------------------|
| Metatropic dysplasia                          | AD   | 12q24.1    | TRPV4 | Transient receptor potential cation channel, subfamily V, member 4         |
| Metatropic dysplasia                          | AD   | 12q24.1    | TRPV4 | Transient receptor potential cation channel, subfamily V, member 4         |
| Metatropic dysplasia                          | AD   | 12q24.1    | TRPV4 | Transient receptor potential cation channel, subfamily V, member 4         |

Short-ribs dysplasias (with or without polydactyly) group

| Condition                                      | Mode | Chromosome | Gene | Description                                                                 |
|------------------------------------------------|------|------------|------|-----------------------------------------------------------------------------|
| Chondroectodermal dysplasia (Ellis—van Creveld) | AR   | 4p16       | EVC1  | EvC gene 1                                                                  |
| Short rib—polydactyly syndrome (SRPS) type 1/3 [Saldino-Noonan/Verma-Naumoff] | AR   | 4p16       | EVC2  | EvC gene 2                                                                  |
| SRPS type 1/3 [Saldino-Noonan/Verma-Naumoff]  | AR   | 11q22.3    | DYNC2H1 | Dynein, cytoplasmic 2, heavy chain 1                                       |
| SRPS type 1/3 [Saldino-Noonan/Verma-Naumoff]  | AR   | 3q25.33    | IFT80 | Intraflagellar transport 80 (homolog of)                                   |
| SRPS type 2 [Majewski]                        | AR   | 4p16       | EVC1  | EvC gene 2                                                                  |
| SRPS type 2 [Majewski]                        | AR   | 4p16       | EVC1  | EvC gene 2                                                                  |

Unlinked to either DYNC2H1 or IFT80.
| Group/name of disorder                                           | Inheritance | MIM No. | Locus   | Gene    | Protein                                                                 | Notes                                                                 |
|-----------------------------------------------------------------|-------------|---------|---------|---------|------------------------------------------------------------------------|----------------------------------------------------------------------|
| SRPS type 4 (Beemer)                                             | AR          | 269860  |         |         |                                                                        |                                                                      |
| Oral-facial-digital syndrome type 4 (Mohr–Majewski)             | AR          | 258860  |         |         |                                                                        |                                                                      |
| Asphyxiating thoracic dysplasia (ATD; Jeune)                    | AR          | 208500  | 3q25.33 | IFT80   | Intraflagellar transport 80 (homolog of)                               |                                                                      |
| Asphyxiating thoracic dysplasia (ATD; Jeune)                    | AR          | 208500  | 11q22.3 | DYNC2H1 | Dynein, cytoplasmic 2, heavy chain                                      | Unlinked to either DYNC2H1 or IFT80                                  |
| Asphyxiating thoracic dysplasia (ATD; Jeune)                    | AR          | 208500  |         |         |                                                                        |                                                                      |
| Thoracolaryngopelvic dysplasia (Barnes)                         | AD          | 187760  |         |         |                                                                        |                                                                      |

See also paternal UPD14 and cerebro-costo-mandibular syndrome

10. Multiple epiphyseal dysplasia and pseudoachondroplasia group

| Pseudoachondroplasia (PSACH)                                     | AD          | 177170  | 19p12–13.1 | COMP | COMP                                                                  |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 1 (EDM1)                | AD          | 132400  | 19p13.1   | COMP | COMP                                                                  |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 2 (EDM2)                | AD          | 600204  | 1p32.2–33 | COL9A2 | Collagen 9 alpha-2 chain                                               |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 3 (EDM3)                | AD          | 600969  | 20q13.3   | COL9A3 | Collagen 9 alpha-3 chain                                               |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 5 (EDM5)                | AD          | 607078  | 2p23–24   | MATN3 | Matrilin 3                                                            |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 6 (EDM6)                | AD          | 120210  | 6q13      | COL9A1 | Collagen 9 alpha-1 chain                                               |                                                                      |
| Multiple epiphyseal dysplasia (MED), other types                 |             |         |           |       |                                                                        | Some MED-like cases unlinked to known genes                           |
| Stickler syndrome, recessive type                               | AR          | 120210  | 6q13      | COL9A1 | Collagen 9 alpha-1 chain                                               |                                                                      |
| Familial hip dysplasia (Beukes)                                 | AD          | 142669  | 4q35      |       |                                                                        |                                                                      |
| Multiple epiphyseal dysplasia with microcephaly and nystagmus   | AR          | 226960  |           |       |                                                                        |                                                                      |
| (Lowry-Wood)                                                    |             |         |           |       |                                                                        |                                                                      |

See also multiple epiphyseal dysplasia, recessive type (rMED, EDM4) in sulfation disorders (group 4), familial osteochondritis dissecans in the aggrecan group, as well as ASPED in the Acromelic group

11. Metaphyseal dysplasias

| Metaphyseal dysplasia, Schmid type (MCS)                         | AD          | 156500  | 6q21–22.3 | COL10A1 | Collagen 10 alpha-1 chain                                              | Includes anauxetic dysplasia                                         |
| Carilage-hair hypoplasia (CHH; metaphyseal dysplasia, McKusick type) | AR          | 250250  | 9p13     | RMRP   | RNA component of RNAse H                                               |                                                                      |
| Metaphyseal dysplasia, Jansen type                               | AD          | 156400  | 3p22–21.1 | PTHR1  | PTH/PTHrP receptor 1                                                   | Activating mutations—see also Blomstrand dysplasia (group 22, 23)   |
| Eiken dysplasia                                                  | AR          | 600002  | 3p22–21.1 | PTHR1  | PTH/PTHrP receptor 1                                                   | Activating mutations—see also Blomstrand dysplasia (group 22, 23)   |
| Disorder                                                                 | Mode of Inheritance | Chromosome | Gene       | Protein/Protein Product                                      |
|-------------------------------------------------------------------------|---------------------|------------|------------|--------------------------------------------------------------|
| Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia [Shwachman–Bodian–Diamond syndrome, SBDS] | AR                  | 7q11       | SBDS       | SBDS protein                                                |
| Metaphyseal anadysplasia type 1                                         | AD, AR              | 11q22.2    | MMP13      | Matrix metalloproteinase 13                                  |
| Metaphyseal anadysplasia type 2                                         | AR                  | 20q13.12   | MMP9       | Matrix metalloproteinase 9                                   |
| Metaphyseal dysplasia, Spahr type                                       | AR                  | 250400     |            |                                                              |
| Metaphyseal acroscyphodysplasia (various types)                        | AR                  | 250215     |            |                                                              |
| Genochondromatosis (type 1/type 2)                                      | AD/SP               | 137360     |            |                                                              |
| Metaphyseal chondromatosis with l-2-hydroxyglutaric aciduria            | AR/SP               | 271550     |            |                                                              |

12. **Spondylometaphyseal dysplasias (SMD)**

| Disorder                                                                 | Mode of Inheritance | Chromosome | Gene       | Protein/Protein Product                                      |
|-------------------------------------------------------------------------|---------------------|------------|------------|--------------------------------------------------------------|
| Spondyloenchondro dysplasia (SPENCD)                                    | AR                  | 19p13.2    | ACP5       | Tartrate-resistant acid phosphatase (TRAP)                   |
| Odontoenchondro dysplasia (ODCD)                                        | AR                  | 184260     |            |                                                              |
| Spondylometaphyseal dysplasia, Sutcliffe type or corner fractures type   | AD                   | 184255     |            |                                                              |
| SMD with severe genu valgum                                              | AD                   | 184253     |            |                                                              |
| SMD with cone-rod dystrophy                                             | AR                  | 608940     |            |                                                              |
| SMD with retinal degeneration, axial type                               | AR/SP               | 602271     |            |                                                              |
| Dysypondyloenchondromatosis                                             | SP                  |            |            |                                                              |
| Cheiro-spondyloenchondromatosis                                         | SP                  |            |            |                                                              |

See also SMD Kozlowski (group TRPV4) disorders in group 11 as well as SMD Sedaghatian type in group 12; there are many individual reports of SMD variants

13. **Spondylo-epi-(meta)-physeal dysplasias (SE(M)D)**

| Disorder                                                                 | Mode of Inheritance | Chromosome | Gene       | Protein/Protein Product                                      |
|-------------------------------------------------------------------------|---------------------|------------|------------|--------------------------------------------------------------|
| Dyggve–Melchior–Clausen dysplasia [DMC]                                   | AR                  | 18q12–21.1 | DYM        | Dymeclin                                                     |
| Immuno-osseous dysplasia [Schimke]                                       | AR                  | 2q34–36    | SMARCAL1   | SWI/SNF-related regulator of chromatin subfamily A-like protein 1 |
| SED, Wolcott–Rallison type                                              | AR                  | 2p12       | EIF2AK3    | Translation initiation factor 2-alpha kinase-3               |
| SEDM, Matrilin type                                                     | AR                  | 2p23–p24   | MATN3      | Matrilin 3                                                   |
| SEDM, short limb—abnormal calcification type                            | AR                  | 1q23       | ODR2       | Discoidin domain receptor family, member 2                   |
| SED tarda, X-linked [SED-XL]                                             | XLR                 | Xp22       | SEDL       | Sedlin                                                       |
| Spondylo-megaepiphysseal-metaphyseal dysplasia (SMMDD)                   | AR                  | 4p16.1     | NKX3-2     | NK3 Homeobox 2                                               |

See also matrilin-related MED in group 8; see also other dysplasias with stippling in group 20

(Continued)
### Severe spondylodysplastic dysplasias

| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Spondylometaphyseal dysplasia, Sedaghatian type | AR | 250220 | | | | |
| Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like) | AR | 7q11 | | SBDS | SBDS gene, function still unclear | |

See also Thanatophoric dysplasia, types 1 and 2 (group 1); ACG2 and Torrance dysplasia (group 2); Fibrochondrogenesis (group 3); Achondrogenesis type 1B (ACG1B, group 4); and Metatropic dysplasia (TRPV4 group)

### Acromelic dysplasias

| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Trichorhinophalangeal dysplasia types 1/3 | AD | 190350 | 8q24 | TRPS1 | Zinc finger transcription factor | Microdeletion syndrome; see also Multiple Cartilagineous Exostoses in group 28 |
| Trichorhinophalangeal dysplasia type 2 [Langer–Giedion] | AD | 150230 | 8q24 | TRPS1 and EXT1 | Zinc finger transcription factor and Exostosin 1 | |
| Acrocapitofemoral dysplasia | AR | 607778 | 2q33–q35 | IHH | Indian hedgehog | |
| Cranioectodermal dysplasia [Levin–Sensenbrenner] type 1 | AR | 218330 | 3q21 | IFT122 | Intraflagellar transport 122 [Chlamydomonas, homolog of | |
| Cranioectodermal dysplasia [Levin–Sensenbrenner] type 2 | AR | 613610 | 2p24.1 | WDR35 | WD repeat-containing protein 35 | |

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**TABLE I (Continued)**

| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Spondylometaphyseal dysplasia, Sedaghatian type | AR | 250220 | | | | |
| Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like) | AR | 7q11 | | SBDS | SBDS gene, function still unclear | |

See also Thanatophoric dysplasia, types 1 and 2 (group 1); ACG2 and Torrance dysplasia (group 2); Fibrochondrogenesis (group 3); Achondrogenesis type 1B (ACG1B, group 4); and Metatropic dysplasia (TRPV4 group)
| Disorder | Mode of Inheritance | Chromosome Location | Gene(s) | Description |
|----------|---------------------|---------------------|---------|-------------|
| Geleophysic dysplasia | AR | 231050 9q34.2 | ADAMTSL2 | ADAMTS-like protein 2 |
| Geleophysic dysplasia, other types | AR | 102370 | | |
| Acromicric dysplasia | AR | 266920 | | |
| Acrodysostosis | AD | 101800 | | |
| Angel-shaped phalango-epiphyseal dysplasia (ASPED) | AD | 105835 | | |
| Saldino–Mainzer dysplasia | AR | 200700 20q11.2 | GDF5 | |
| Acromesomelic dysplasia type Maroteaux (AMDM) | AR | 602875 9p13–12 | NPR2 | Natriuretic peptide receptor 2 |
| Grebe dysplasia | AR | 200700 20q11.2 | GDF5 | Growth and differentiation factor 5 |
| Papillon-Lefèvre syndrome | AD | 228900 20q11.2 | GDF5 | Growth and differentiation factor 5 |
| Acromesomelic dysplasia with genital anomalies | AR | 609441 4q23–24 | BMPR1B | Bone morphogenetic protein receptor 1B |
| Acromesomelic dysplasia, Osebold-Remondini type | AD | 609441 4q23–24 | BMPR1B | Bone morphogenetic protein receptor 1B |
| Fibular hypoplasia and complex brachydactyly (Du Pan) | AR | 228900 20q11.2 | GDF5 | Growth and differentiation factor 5 |
| Acromesomelic dysplasia, Osebold-Remondini type | AD | 609441 4q23–24 | BMPR1B | Bone morphogenetic protein receptor 1B |
| Dyschondrosteosis (Leri–Weill) | Pseudo-AD | 127300 Xpter-p22.32 | SHOX | Short stature—homeobox gene |
| Langer type (homozygous dyschondrosteosis) | Pseudo-AR | 249700 Xpter-p22.32 | SHOX | Short stature—homeobox gene |
| Omodyslasia | AR | 258315 13q31–q32 | GPC6 | Glypican 6 |
| Robinow syndrome, recessive type | AR | 268310 9q22 | ROR2 | Receptor tyrosine kinase-like orphan receptor 2 |
| Robinow syndrome, dominant type | AD | 180700 2q24–32 | HOXD | Duplication in HOXD gene cluster |
| Mesomelic dysplasia, Korean type | AD | 156232 2q24–32 | HOXD | Duplications in HOXD gene cluster |
| Mesomelic dysplasia, Kozlowski-Reardon type | AD | 249710 | | |
| Mesomelic dysplasia with acral synostoses (Verloes–David–Pfeiffer type) | AD | 600383 8q13 | SULF1 and SLC5A1 | Heparan sulfate 6-O-endosulfatase 1 and solute carrier organic anion transporter family member 5A1 |

(Continued)
| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Mesomelic dysplasia, Savarirayan type (Triangular Tibia–Fibular Aplasia) | SP | 605274 | | | | |
| 18. Bent bones dysplasias | | | | | | |
| Campomelic dysplasia (CD) | AD | 114290 | 17q24.3–25.1 | SOX9 | SRY-box 9 | Includes acampomelic campomelic dysplasia (ACD) as well as mild campomelic dysplasia (MIM 602196) |
| Stüve–Wiedemann dysplasia | AR | 601559 | 5p13.1 | LIFR | Leukemia inhibitory factor receptor | |
| Kyphomelic dysplasia, several forms | | 211350 | | | | Probably heterogeneous |

Bent bones at birth can be seen in a variety of conditions, including osteogenesis imperfecta, Antley–Bixler syndrome, cartilage-hair hypoplasia, Cummings syndrome, hypophosphatasia, dyssegmental dysplasia, TD, ATD, and others

19. Slender bone dysplasia group

| 3-M syndrome (3M1) | AR | 273750 | 6p21.1 | CUL7 | Culin 7 | Includes dolichospondylic dysplasia and Yakut short stature syndrome |
| 3-M syndrome (3M2) | AR | 612921 | 2q35 | OBSL1 | Obscurin-like 1 | |
| Kenny–Caffey dysplasia type 1 | AR | 244460 | 1q42–q43 | TBCE | Tubulin-specific chaperone E | Includes Taub–Linder cephaloskeletal dysplasia |
| Kenny–Caffey dysplasia type 2 | AD | 127000 | | | | |
| Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1) | AR | 210710 | 2q | | | |
| Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type) | AR | 210720 | 21q | PCNT2 | Pericentrin 2 | |
| IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies) | XL/AD | 300290 | | | | Possibly heterogeneous |
| Osteocraniostenosis | SP | 602361 | | | | Occurrence in sibs reported, inheritance unclear |
| Hallermann–Streiff syndrome | AR | 234100 | | | | Mutations in GJA1 reported in one case only |

See also Cerebro-arthro-digital dysplasia

20. Dysplasias with multiple joint dislocations

| Desbuquois dysplasia (with accessory ossification center in digit 2) | AR | 251450 | 17q25.3 | CANT1 | |
| Desbuquois dysplasia with short metacarpals and elongated phalanges (Kim type) | AR | 251450 | 17q25.3 | CANT1 | |
### 21. Chondrodysplasia punctata (CDP) group

| CDP Type | Inheritance | Chromosome | Gene | Description |
|----------|-------------|-------------|------|-------------|
| CDP, X-linked dominant, Conradi–Hünermann type (CDPX2) | XLD | Xp11 | EBP | Emopamil-binding protein |
| CDP, X-linked recessive, brachytelephalangic type (CDPX1) | XLR | Xp22.3 | ARSE | Arylsulfatase E |
| Congenital hemidysplasia, ichthyosis, limb defects (CHST3) | XLD | Xp11 | NSDHL | NAD[P]H steroid dehydrogenase-like protein |
| Congenital hemidysplasia, ichthyosis, limb defects (CHST3) | XLD | Xq28 | EBP | Emopamil-binding protein |
| Greenberg dysplasia | AR | 1q42.1 | LBR | Lamin B receptor, 3-beta-hydroxysterol delta (14)-reductase |
| Rhizomelic CDP type 1 | AR | 6q22–24 | PEX7 | Peroxisomal PTS2 receptor |
| Rhizomelic CDP type 2 | AR | 1q42 | DHPAT | Dihydroxyacetonephosphate acyltransferase (DHAPAT) |
| Rhizomelic CDP type 3 | AR | 2q31 | AGPS | Alkylglycerone-phosphate synthase (AGPS) |
| CDP tibial-metacarpal type | AD/AR | 118651 | EBP | Emopamil-binding protein |
| Astley-Kendall dysplasia | AR? | 118651 | | |

Note that stippling can occur in several syndromes such as Zellweger, Smith–Lemli–Opitz and others. See also desmosterolosis as well as SEMD short limb—abnormal calcification type in group 11.

### 22. Neonatal osteosclerotic dysplasias

| Dysplasia | Inheritance | Chromosome | Gene | Description |
|-----------|-------------|-------------|------|-------------|
| Blomstrand dysplasia | AR | 3p22–21.1 | PTH1 | PTH/PTHrP receptor 1 |
| Desmosterolosis | AR | 1p33 | DHCR24 | 3-beta-hydroxysterol delta-24-reductase |
| Caffey disease (including infantile and attenuated forms) | AD | 17q21–22 | COL1A1 | Collagen 1, alpha-1 chain |
| Caffey disease (severe variants with prenatal onset) | AR | 11q13 | TCIRG1 | Subunit of ATPase proton pump |
| Raine dysplasia (lethal and non-lethal forms) | AR | 7q22 | FAM20C | Includes lethal and non-lethal cases |

See also Astley-Kendall dysplasia and CDPs in group 21.

### 23. Increased bone density group (without modification of bone shape)

| Dysplasia | Inheritance | Chromosome | Gene | Description |
|-----------|-------------|-------------|------|-------------|
| Osteopetrosis, severe neonatal or infantile forms (OPTB1) | AR | 11q13 | TCIRG1 | Subunit of ATPase proton pump |
| Osteopetrosis, severe neonatal or infantile forms (OPTB4) | AR | 16p13 | CLC7 | Chloride channel 7 |

(Continued)
| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Osteopetrosis, infantile form, with nervous system involvement (OPTB5) | AR | 259720 | 6q21 | OSTM1 | Gray lethal/osteopetrosis associated transmembrane protein | |
| Osteopetrosis, intermediate form, osteoclast-poor (OPTB2) | AR | 259710 | 13q14.11 | RANKL | Receptor activator of NF-kappa-B ligand (tumor necrosis factor ligand superfamily, member 11) | |
| Osteopetrosis, infantile form, osteoclast-poor with immunoglobulin deficiency (OPTB7) | AR | 612302 | 18q21.33 | RANK | Receptor activator of NF-kappa-B | See also familial expansile osteolysis in Osteolysis group (group 28) |
| Osteopetrosis, intermediate form (OPTB6) | AR | 611497 | 17q21.3 | PLEKH1 | Pleckstrin homology domain-containing protein, family M, member 1 | Chloride channel pump |
| Osteopetrosis, intermediate form (OPTA2) | AR | 259710 | 16p13 | CLCN7 | Chloride channel pump | Carbonic anhydrase 2 |
| Osteopetrosis with renal tubular acidosis (OPTB3) | AR | 259730 | 8q22 | CA2 | Low density lipoprotein receptor-related protein 5 | Includes Worth type osteosclerosis (MIM 144750) |
| Osteopetrosis, late-onset form type 1 (OPTA1) | AD | 607634 | 11q13.4 | LRP5 | | Chloride channel 7 |
| Osteopetrosis, late-onset form type 2 (OPTA2) | AD | 166600 | 16p13 | CLCN7 | | |
| Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID) | XL | 300301 | Xq28 | IKBKG | Inhibitor of kappa light polypeptide gene enhancer, kinase of | |
| Osteopetrosis, moderate form with defective leucocyte adhesion (LAD3) | AR | 612840 | 11q12 | FERMT3 | | Includes Buschke–Ollendorff syndrome (MIM 166700) |
| Osteopetrosis, moderate form with defective leucocyte adhesion | AR | 612840 | 11q13 | RASGRP2 | Ras guanyl nucleotide-releasing protein 2 | Includes mixed sclerosing bone dysplasia |
| Pyknody sostosis | AR | 265800 | 1q21 | CTSK | Cathepsin K | |
| Osteopoikilosis | AD | 155950 | 12q14 | LEMD3 | LEM domain-containing | |
| Melorheostosis with osteopoikilosis | AD | 155950 | 12q14 | LEMD3 | LEM domain-containing | |
| Osteopatia striata with cranial sclerosis (OSCS) | XLD | 300373 | Xq11.1 | WTX | FAM123B | No germ line LEMD3 mutations identified so far |
| Melorheostosis | SP | | | | | Possibly related to “osteosclerotic metaphyseal dysplasia” |
| Dysosteosclerosis | AR | 224300 | | | | |
| Osteomesopyknosis | AD | 166450 | | | | Same as osteopetrosis with nervous system involvement (see above)? |
| Osteopetrosis with infantile neuroaxonal dysplasia | AR? | 600329 | | | | |
### 24. Increased bone density group with metaphyseal and/or diaphyseal involvement

| Disorder                                      | Mode | Chromosome | Gene(s)                  | Description                                                                 |
|-----------------------------------------------|------|------------|--------------------------|-----------------------------------------------------------------------------|
| Craniometaphyseal dysplasia, autosomal dominant type | AD   | 5p15.2–14.2| ANKH                     | Homolog of mouse ANK (ankylosis) gene Gain of function mutations            |
| Diaphyseal dysplasia                          | AD   | 19q13      | TGFbeta1                 | Transforming growth factor beta 1                                            |
| Camurati-Engelmann                            | AD   | 7q34       | TBXAS1                   | Thromboxane A synthase 1                                                   |
| Hematodiaphyseal dysplasia Ghosal             | AR   | 4q34–35    | HPGD                     | 15-alpha-hydroxyprostaglandin dehydrogenase Includes cranio-osteoarthropathy and cases of recessive pachydermoperiostosis Relationship to recessive form (MIM 259100, HPGD deficiency) unclear |
| Hypertrophic osteoarthropathy                 | AR   | 6q22–23    | GJA1                     | Gap junction protein alpha-1                                                |
| Pachydermoperiostosis                        | AD   | 17q21      | DLX3                     | Distal-less homeobox 3                                                      |
| Oculo-dentesosseous dysplasia (0000) mild type| AD   | 6q22–23    | SOST                     | Sclerostin                                                                  |
| Oculo-dentesosseous dysplasia (0000) severe type| AR  | 6q22–23    | SOST                     | Sclerostin                                                                  |
| Osteoectasia with hyperphosphatasia           | AR   | 8q24       | OPG                      | Osteoprotegerin                                                            |
| Sclerosteosis                                 | AR   | 17q12–21   | SOST                     | Sclerostin                                                                  |
| Endosteal hyperostosis, van Buchem type       | AR   | 17q12–21   | SOST                     | Sclerostin                                                                  |
| Trichodentesosseous dysplasia                 | AD   | 17q21      | DLX3                     | Distal-less homeobox 3                                                      |
| Cranio-metaphyseal dysplasia, autosomal recessive type | AR | 6q21–22 | SOST                     | Sclerostin                                                                  |
| Diaphyseal medullary stenosis with bone malignancy | AD | 9q24       | OPG                      | Osteoprotegerin                                                            |
| Pyle disease                                  | AR   | 9p21–p22   | SOST                     | Sclerostin                                                                  |
| Lenz–Majewski hyperostotic dysplasia          | SP   | 15q10      | SOST                     | Sclerostin                                                                  |
| Metaphyseal dysplasia, Braun–Tischert type    | XL   | 605946     | SOST                     | Sclerostin                                                                  |

### 25. Osteogenesis imperfecta and decreased bone density group

For comments the classification of osteogenesis imperfecta, please refer to the text

For osteogenesis imperfecta, non-deforming form (OI type 1)

| Disorder                                      | Mode | Chromosome | Gene(s)                  | Description                                                                 |
|-----------------------------------------------|------|------------|--------------------------|-----------------------------------------------------------------------------|
| Osteogenesis imperfecta                       | AD   | 5p15.2–14.2| ANKH                     | Homolog of mouse ANK (ankylosis) gene Gain of function mutations            |
| Osteogenesis imperfecta, perinatal lethal form (OI type 2) | AD, AR | 19q13      | TGFbeta1                 | Transforming growth factor beta 1                                            |
| Osteogenesis imperfecta, progressively deforming type (OI type 3) | AD, AR | 7q34       | TBXAS1                   | Thromboxane A synthase 1                                                   |
| Osteogenesis imperfecta, moderate form (OI type 4) | AD, AR | 4q34–35    | HPGD                     | 15-alpha-hydroxyprostaglandin dehydrogenase Includes cranio-osteoarthropathy and cases of recessive pachydermoperiostosis Relationship to recessive form (MIM 259100, HPGD deficiency) unclear |

For osteogenesis imperfecta, perinatal lethal form (OI type 2)

| Disorder                                      | Mode | Chromosome | Gene(s)                  | Description                                                                 |
|-----------------------------------------------|------|------------|--------------------------|-----------------------------------------------------------------------------|
| Osteogenesis imperfecta                       | AD   | 5p15.2–14.2| ANKH                     | Homolog of mouse ANK (ankylosis) gene Gain of function mutations            |
| Osteogenesis imperfecta, perinatal lethal form (OI type 2) | AD, AR | 19q13      | TGFbeta1                 | Transforming growth factor beta 1                                            |
| Osteogenesis imperfecta, progressively deforming type (OI type 3) | AD, AR | 7q34       | TBXAS1                   | Thromboxane A synthase 1                                                   |
| Osteogenesis imperfecta, moderate form (OI type 4) | AD, AR | 4q34–35    | HPGD                     | 15-alpha-hydroxyprostaglandin dehydrogenase Includes cranio-osteoarthropathy and cases of recessive pachydermoperiostosis Relationship to recessive form (MIM 259100, HPGD deficiency) unclear |

See also Bruck syndrome type 1 (below)

For osteogenesis imperfecta, progressively deforming type (OI type 3)

| Disorder                                      | Mode | Chromosome | Gene(s)                  | Description                                                                 |
|-----------------------------------------------|------|------------|--------------------------|-----------------------------------------------------------------------------|
| Osteogenesis imperfecta                       | AD   | 5p15.2–14.2| ANKH                     | Homolog of mouse ANK (ankylosis) gene Gain of function mutations            |
| Osteogenesis imperfecta, perinatal lethal form (OI type 2) | AD, AR | 19q13      | TGFbeta1                 | Transforming growth factor beta 1                                            |
| Osteogenesis imperfecta, progressively deforming type (OI type 3) | AD, AR | 7q34       | TBXAS1                   | Thromboxane A synthase 1                                                   |
| Osteogenesis imperfecta, moderate form (OI type 4) | AD, AR | 4q34–35    | HPGD                     | 15-alpha-hydroxyprostaglandin dehydrogenase Includes cranio-osteoarthropathy and cases of recessive pachydermoperiostosis Relationship to recessive form (MIM 259100, HPGD deficiency) unclear |

For osteogenesis imperfecta, moderate form (OI type 4)

| Disorder                                      | Mode | Chromosome | Gene(s)                  | Description                                                                 |
|-----------------------------------------------|------|------------|--------------------------|-----------------------------------------------------------------------------|
| Osteogenesis imperfecta                       | AD   | 5p15.2–14.2| ANKH                     | Homolog of mouse ANK (ankylosis) gene Gain of function mutations            |
| Osteogenesis imperfecta, perinatal lethal form (OI type 2) | AD, AR | 19q13      | TGFbeta1                 | Transforming growth factor beta 1                                            |
| Osteogenesis imperfecta, progressively deforming type (OI type 3) | AD, AR | 7q34       | TBXAS1                   | Thromboxane A synthase 1                                                   |
| Osteogenesis imperfecta, moderate form (OI type 4) | AD, AR | 4q34–35    | HPGD                     | 15-alpha-hydroxyprostaglandin dehydrogenase Includes cranio-osteoarthropathy and cases of recessive pachydermoperiostosis Relationship to recessive form (MIM 259100, HPGD deficiency) unclear |

See also Bruck syndrome type 1 (below)
| Group/name of disorder                                                                 | Inheritance | MIM No. | Locus  | Gene   | Protein                                                                 | Notes                                                                 |
|--------------------------------------------------------------------------------------|-------------|---------|--------|--------|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus (OI type 5) | AD          | 610967  |        |        |                                                                         |                                                                      |
| Osteogenesis imperfecta, other types<br> Bruck syndrome type 1 (BS1)                  | AR          | 259450  | 17q21  | FKBP10 | FK506 binding protein 10                                               | See autosomal recessive OI, above; intrafamilial variability between OI3 and BS1 documented |
| Bruck syndrome type 2 (BS2)                                                          | AR          | 609220  | 3q23–24| PLOD2  | Procollagen lysyl hydroxylase 2                                          |                                                                      |
| Osteoporosis-pseudoglioma syndrome                                                   | AR          | 259770  | 11q12–13| LRP5   | LDL-receptor related protein 5                                           |                                                                      |
| Calvarial doughnut lesions with bone fragility<br> Idiopathic juvenile osteoporosis   | AD          | 126550  |        |        |                                                                         | Some patients reported with heterozygous mutations in the LRP5 gene  |
| Cole-Carpenter dysplasia (bone fragility with craniosynostosis)                      | SP          | 112240  |        |        |                                                                         | See also craniosynostosis syndromes in group 30                      |
| Spondylo-ocular dysplasia                                                             | AR          | 605822  |        |        |                                                                         | Unlinked to collagen 1 and collagen 2 genes or LRP5                  |
| Osteopenia with radiolucent lesions of the mandible<br> Ehlers–Danlos syndrome, progeroid form | AR          | 130070  | 5q35   | B4GALT7| Xylosylprotein 4-beta-galactosyltransferase deficiency                   |                                                                      |
| Geroderma osteodysplasticum<br> Cutis laxa, autosomal recessive form, type 2B (ARCL2B) | AR          | 231070  | 1q24.2 | GORAB  | SCYL1-binding protein 1                                                  | Skeletal features overlapping with progeroid EDS and geroderma osteodysplasticum |
|                                                                                      | AR          | 612940  | 17q25.3| PYCR1  | Pyrroline-5-carboxylate reductase 1                                     |                                                                      |
| Cutis laxa, autosomal recessive form, type 2A (ARCL2A) (Wrinkly skin syndrome)      | AR          | 278250,  | 12q24.3| ATP6V0A2| ATPase, H+ transporting, lysosomal, V0 subunit A2                       | Skeletal features overlapping with progeroid EDS and geroderma osteodysplasticum |
|                                                                                     |             | 219200  |        |        |                                                                         |                                                                      |
| Singleton–Merten dysplasia                                                           | AD          | 182250  |        |        |                                                                         |                                                                      |
| 26. Abnormal mineralization group                                                    |             |         |        |        |                                                                         |                                                                      |
| Hypophosphatasia, perinatal lethal and infantile forms                               | AR          | 241500  | 1p36.1–p34| ALPL  | Alkaline phosphatase, tissue non-specific (TNSALP)                      | Intrafamilial variability                                           |
| Hypophosphatasia, adult form                                                         | AD          | 146300  | 1p36.1–p34| ALPL  | Alkaline phosphatase, tissue non-specific (TNSALP)                      | Includes odontohipophosphatasia                                     |
| Condition                                                                 | Type   | Chromosome | Gene       | Description                                                                 |
|---------------------------------------------------------------------------|--------|------------|------------|-----------------------------------------------------------------------------|
| Hypophosphatemic rickets, X-linked dominant                               | XLD    | Xp22       | PHEX       | X-linked hypophosphatemia membrane protease                               |
| Hypophosphatemic rickets, autosomal dominant                              | AD     | 12p13.3    | FGF23      | Fibroblast growth factor 23                                               |
| Hypophosphatemic rickets, autosomal recessive, type 1 (ARHR1)            | AR     | 4q21       | DMP1       | Dentin matrix acidic phosphoprotein 1                                    |
| Hypophosphatemic rickets, autosomal recessive, type 2 (ARHR2)            | AR     | 6q23       | ENPP1      | Ectonucleotide pyrophosphatase/phosphodiesterase 1                         |
| Hypophosphatemic rickets with hypercalcuiuria, X-linked recessive        | XLR    | Xp11.22    | CLCN5      | Chloride channel 5                                                        |
| Hypophosphatemic rickets with hypercalcuiuria, autosomal recessive        | AR     | 9q34       | SLC34A3    | Sodium-phosphate cotransporter                                            |
| Neonatal hyperparathyroidism, severe form                                 | AR     | 3q13.3–21  | CASR       | Calcium-sensing receptor                                                  |
| Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism | AD     | 3q13.3–21  | CASR       | Calcium-sensing receptor                                                  |
| Calcium pyrophosphate deposition disease [familial chondrocalcinosis] type 2 | AD     | 5p15.2–14.2| ANKH       | Homolog of mouse ANK (ankylosis) gene                                     |
|                                                                         |        |            |            | Loss of function mutations [see craniometaphyseal dysplasia in group 24]    |
| See also Jansen dysplasia and Eiken dysplasia                             |        |            |            |                                                                             |
| 27. Lysosomal storage diseases with skeletal involvement [dysostosis multiplex group] |        |            |            |                                                                             |
| Mucopolysaccharidosis type 1H/1S                                           | AR     | 4p16.3     | IDA        | Alpha-1-iduronidase                                                        |
| Mucopolysaccharidosis type 2                                              | XLR    | 4q27.3–28  | IDS        | Iduronate-2-sulfatase                                                      |
| Mucopolysaccharidosis type 3A                                             | AR     | 17q25.3    | HSS        | Heparan sulfate sulfatase                                                 |
| Mucopolysaccharidosis type 3B                                             | AR     | 17q21      | NAGLU      | N-Ac-beta-D-glucosaminidase                                               |
| Mucopolysaccharidosis type 3C                                             | AR     | 8p11–q13   | HSGNAT     | Ac-CoA alpha-glucosaminide N-acetyltransferase                            |
| Mucopolysaccharidosis type 3D                                             | AR     | 12q14      | GNS        | N-Acetylglucosamine 6-sulfatase                                           |
| Mucopolysaccharidosis type 4A                                             | AR     | 16q24.3    | GALNS      | Galactosamine-6-sulfatase                                                 |
| Mucopolysaccharidosis type 4B                                             | AR     | 3p21.33    | GLBI       | beta-Galactosidase                                                        |
| Mucopolysaccharidosis type 5                                              | AR     | 5q13.3     | ARSB       | Arylsulfatase B                                                           |
| Mucopolysaccharidosis type 7                                              | AR     | 7q21.11    | GUSB       | beta-Glucuronidase                                                        |
| Fucosidosis                                                               | AR     | 1p34       | FUCA       | alpha-Fucosidase                                                          |
| alpha-Mannosidosis                                                        | AR     | 19p13.2–12 | MANA       | alpha-Mannosidase                                                         |
| beta-Mannosidosis                                                        | AR     | 4q22–25    | MANB       | beta-Mannosidase                                                          |
| Aspartylglucosaminuria                                                    | AR     | 4q23–27    | AGA        | Aspartyl-glucosaminidase                                                  |
| GM1 Gangliosidosis, several forms                                         | AR     | 4p21–14.2  | GB1        | beta-Galactosidase                                                        |
| Sialidosis, several forms                                                | AR     | 6p21.3     | NEU1       | Neuaminidase [sialidase]                                                   |
| Sialic acid storage disease [SIASD], several forms                       | AR     | 6q14–q15   | SLC17A5    | Sialin [sialic acid transporter]                                          |
| Galactosialidosis, several forms                                         | AR     | 20q13.1    | PPGB       | beta-Galactosidase protective protein                                     |
| Multiple sulfatase deficiency                                            | AR     | 3p26       | SUMF1      | Sulfatase-modifying factor-1                                              |
| Mucolipidosis II [I-cell disease], alpha/beta type                       | AR     | 4q21–23    | GNPTAB     | N-Acetylgalcosamine 1-phosphotransferase, alpha/beta subunits              |

(Continued)
| Group/name of disorder                                                                 | Inheritance | MIM No. | Locus     | Gene                | Protein                                                                 | Notes                                                                 |
|--------------------------------------------------------------------------------------|-------------|---------|-----------|---------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| Mucolipidosis III (Pseudo-Hurler polydystrophy), alpha/beta type                    | AR          | 252600  | 4q21–23   | GNPTAB              | N-Acetylglucosamine 1-phosphotransferase, alpha/beta subunits            |                                                                      |
| Mucolipidosis III (Pseudo-Hurler polydystrophy), gamma type                         | AR          | 252605  | 4q21–23   | GNPTG               | N-Acetylglucosamine 1-phosphotransferase, gamma subunit                 |                                                                      |
| 28. Osteolysis group                                                                  |             |         |           |                     |                                                                         |                                                                      |
| Familial expansile osteolysis                                                        | AD          | 174810  | 18q22.1   | RANK (TNFRSF11A)    |                                                                         | Includes expansile skeletal hyperphosphatasia (MIM 602080)           |
| Mandibuloacral dysplasia type A                                                       | AD          | 248370  | 1q21.2    | LMNA                | Lamin A/C                                                             |                                                                      |
| Mandibuloacral dysplasia type B                                                       | AR          | 608612  | 1p34      | ZMPSTE24            | Zinc metalloproteinase                                                  |                                                                      |
| Progeria, Hutchinson–Gilford type                                                    | AD          | 176670  | 1q21.2    | LMNA                | Lamin A/C                                                             |                                                                      |
| Torg–Winchester syndrome                                                              | AR          | 259600  | 16q13     | MMP2                | Matrix metalloproteinase 2                                             |                                                                      |
| Mandibuloacral dysplasia with leukoencephalopathy (presenile dementia with bone cysts; Nasu–Hakola) | AD          | 102500  |           |                     |                                                                         |                                                                      |
| Lipomembranous osteodystrophy                                                        | AD          | 166300  |           |                     |                                                                         |                                                                      |
| Lipomembranous osteodystrophy with leukoencephalopathy (presenile dementia with bone cysts; Nasu–Hakola) | AR          | 221770  | 6p21.2    | TREM2               | Triggering receptor expressed on myeloid cells 2                        |                                                                      |
| Lipomembranous osteodystrophy with leukoencephalopathy (presenile dementia with bone cysts; Nasu–Hakola) | AR          | 221770  | 19q13.1   | TYROBP              | Tyro protein tyrosine kinase-binding protein                              |                                                                      |
| Hajdu–Cheney syndrome                                                                | AD          | 102500  |           |                     |                                                                         |                                                                      |
| Multicentric carpal–tarsal osteolysis with and without nephropathy                   | AD          | 166300  |           |                     |                                                                         |                                                                      |
| Lipomembranous osteodystrophy                                                        | AR          | 221770  | 6p21.2    | TREM2               | Triggering receptor expressed on myeloid cells 2                        |                                                                      |
| Lipomembranous osteodystrophy with leukoencephalopathy (presenile dementia with bone cysts; Nasu–Hakola) | AR          | 221770  | 19q13.1   | TYROBP              | Tyro protein tyrosine kinase-binding protein                              |                                                                      |

See also Pycnodysostosis, cleidocranial dysplasia, and Singleton–Merten syndrome. Note: several neurologic conditions may cause acroosteolysis.

29. Disorganized development of skeletal components group

| Multiple cartilaginous exostoses 1                                                    | AD          | 133700  | 8q23–24.1 | EXT1                | Exostosin-1                                                            |                                                                      |
| Multiple cartilaginous exostoses 2                                                    | AD          | 133701  | 11p12–11  | EXT2                | Exostosin-2                                                            |                                                                      |
| Multiple cartilaginous exostoses 3                                                    | AD          | 600209  | 19p       | SH3BP2              | SH3 domain-binding protein 2                                           |                                                                      |
| Cherubism                                                                              | AD          | 118400  | 4p16      |                     |                                                                         |                                                                      |
| Fibrous dysplasia, polyostotic form                                                    | SP          | 174800  | 20q13     | GNAS1               | Guanine nucleotide-binding protein, alpha-stimulating activity subunit | Somatic mosaicism and imprinting phenomena; includes McCune–Albright syndrome |
| Progressive osseous heteroplasia                                                       | AD          | 166350  | 20q13     | GNAS1               | Guanine nucleotide-binding protein, alpha-stimulating activity subunit | Gene subject to imprinting                                           |
| Gnathodiaphyseal dysplasia                                                             | AD          | 166260  | 11p15.1–14.3 | TMEM16E | Transmembrane protein 16E                                             |                                                                      |
| Metachondromatosis                                                                     | AD          | 156250  | 12q24     | PTPN11              | Protein-tyrosine phosphatase nonreceptor-type 11                        |                                                                      |
| Disorder                                         | Mode of Inheritance | Chromosome Region | Genes Affected | Comments                                                                 |
|------------------------------------------------|---------------------|-------------------|---------------|--------------------------------------------------------------------------|
| Osteoglophonic dysplasia                        | AD                  | 8p11              | FGFR1         | Fibroblast growth factor receptor 1                                      |
| Fibrodyplasia ossicicans progressiva (FOP)      | AD, SP              | 2q23–24           | ACVR1         | Activin A (BMP type 1) receptor                                          |
| Neurofibromatosis type 1 (NF1)                  | AD                  | 17q11.2           | NF1           | Neurofibromin                                                            |
| Carpotarsal osteochondromatosis                 | AD                  | 12q8.2            |              |                                                                          |
| Cherubism with gingival fibromatosis (Ramon syndrome) | AD                  | 26q22             |              |                                                                          |
| Dysplasia epiphysealis hemimelica (Trevor)      | SP                  | 166000            |              |                                                                          |
| Enchondromatosis (Ollier)                       | SP                  | 166000            |              |                                                                          |
| Enchondromatosis with hemangioma (Maffucci)     | SP                  | 166000            |              |                                                                          |
| Neurofibromatosis type 1 (NF1)                  | AD                  | 5q35              | NSD1          | Nuclear receptor-binding su-var, enhancer of zeste, and trithorax domain protein 1 |
| Marshall–Smith syndrome                         | SP                  | 19p13.3           | NFIX          | Nuclear factor I/X                                                       |
| Proteus syndrome                                | SP                  | 176920            |              |                                                                          |
| Marfan syndrome                                 | AD                  | 15q21.1           | FBN1          | Fibrillin 1                                                              |
| Congenital contractual arachnodactyly           | AD                  | 15q21.1           | FBN2          | Fibrillin 2                                                              |
| Loey–Dietz syndrome types 1A and 2A             | AD                  | 9q22              | TGFBR1        | TGFbeta receptor subunit 1                                              |
| Loey–Dietz syndrome types 1B and 2B             | AD                  | 3p22              | TGFBR2        | TGFbeta receptor subunit 2                                              |
| Overgrowth syndrome with 2q37 translocations    | SP                  | 2q37              | NPPC          | Natriuretic peptide precursor C                                          |
| Overgrowth syndrome with skeletal dysplasia (Nishimura–Schmidt, endochondral gigantism) | SP?                 |                   |              | Overgrowth probably caused by overexpression of NPPC Nosologic status unclear but conspicuous skeletal phenotype(s) |
| Overgrowth syndrome with skeletal dysplasia (Nishimura–Schmidt, endochondral gigantism) | SP?                 |                   |              | Overgrowth probably caused by overexpression of NPPC Nosologic status unclear but conspicuous skeletal phenotype(s) |
| Sotos syndrome                                  | AD                  | 5q35              | NSD1          | Nuclear receptor-binding su-var, enhancer of zeste, and trithorax domain protein 1 |
| Proteus syndrome                                | SP                  | 176920            |              |                                                                          |
| Marfan syndrome                                 | AD                  | 15q21.1           | FBN1          | Fibrillin 1                                                              |
| Congenital contractual arachnodactyly           | AD                  | 15q21.1           | FBN2          | Fibrillin 2                                                              |
| Loey–Dietz syndrome types 1A and 2A             | AD                  | 9q22              | TGFBR1        | TGFbeta receptor subunit 1                                              |
| Loey–Dietz syndrome types 1B and 2B             | AD                  | 3p22              | TGFBR2        | TGFbeta receptor subunit 2                                              |
| Overgrowth syndrome with 2q37 translocations    | SP                  | 2q37              | NPPC          | Natriuretic peptide precursor C                                          |
| Overgrowth syndrome with skeletal dysplasia (Nishimura–Schmidt, endochondral gigantism) | SP?                 |                   |              | Overgrowth probably caused by overexpression of NPPC Nosologic status unclear but conspicuous skeletal phenotype(s) |
| Sotos syndrome                                  | AD                  | 5q35              | NSD1          | Nuclear receptor-binding su-var, enhancer of zeste, and trithorax domain protein 1 |
| Proteus syndrome                                | SP                  | 176920            |              |                                                                          |
| Marfan syndrome                                 | AD                  | 15q21.1           | FBN1          | Fibrillin 1                                                              |
| Congenital contractual arachnodactyly           | AD                  | 15q21.1           | FBN2          | Fibrillin 2                                                              |
| Loey–Dietz syndrome types 1A and 2A             | AD                  | 9q22              | TGFBR1        | TGFbeta receptor subunit 1                                              |
| Loey–Dietz syndrome types 1B and 2B             | AD                  | 3p22              | TGFBR2        | TGFbeta receptor subunit 2                                              |
| Overgrowth syndrome with 2q37 translocations    | SP                  | 2q37              | NPPC          | Natriuretic peptide precursor C                                          |
| Overgrowth syndrome with skeletal dysplasia (Nishimura–Schmidt, endochondral gigantism) | SP?                 |                   |              | Overgrowth probably caused by overexpression of NPPC Nosologic status unclear but conspicuous skeletal phenotype(s) |

See also Sprinzen–Goldberg syndrome in Craniosynostosis group

**31. Genetic inflammatory/rheumatoid-like osteoarthropathies**

| Disorder                                         | Mode of Inheritance | Chromosome Region | Genes Affected | Comments                                                                 |
|------------------------------------------------|---------------------|-------------------|---------------|--------------------------------------------------------------------------|
| Progressive pseudorheumatoid dysplasia (PPRD, SED with progressive arthropathy) | AR                  | 6q22–23           | WISP3         | WNT1-inducible signaling pathway protein 3                               |
| Chronic infantile neurologic cutaneous articular syndrome (CINCA)/neonatal onset multisystem inflammatory disease (NOMID) | AD                  | 1q44              | CIAS1         | Cryopyrin                                                                |

(Continued)
| Group/name of disorder                                                                 | Inheritance | MIM No. | Locus    | Gene    | Protein                                                                 | Notes                                                                 |
|---------------------------------------------------------------------------------------|-------------|---------|----------|---------|------------------------------------------------------------------------|----------------------------------------------------------------------|
| Sterile multifocal osteomyelitis, periostitis, and pustulosis (CINCA/NOMID-like)       | AR          | 147679  | 2q14.2   | IL1RN   | Interleukin 1 receptor antagonist                                       |                                                                      |
| Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anemia (CRMO with CDA; Majeed syndrome) | AR          | 609628  | 18p11.3  | LPIN2   | Lipin 2                                                                |                                                                      |
| Hyperostosis/hyperphosphatemia syndrome                                                | AR          | 610233  | 2q24–q31 | GALNT3  | UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminytransferase 3 |                                                                      |
| Infantile systemic hyalinosis/Juvenile hyaline fibromatosis (ISH/JHF)                  | AR          | 236490  | 4q21     | ANTXR2  | Anthrax toxin receptor 2                                               | Includes Juvenile hyaline fibromatosis (JHF, 228600) and Puretic syndrome |

32. Cleidocranial dysplasia and isolated cranial ossification defects group

| Cleidocranial dysplasia                                                                 | AD          | 119600  | 6p21     | RUNX2   | Runt related transcription factor 2                                    |                                                                      |
| CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate a.u., genital anomalies, skin eruption) | AR          | 603116  | 22q12–q13|         |                                                                        |                                                                      |
| Yunis–Varon dysplasia                                                                  | AR          | 216340  |          |         |                                                                        |                                                                      |
| Parietal foramina (isolated)                                                           | AD          | 168500  | 11q11.2  | ALX4    | Aristaless-like 4                                                     | See also Frontonasal dysplasia type 1 (group 34)                      |
| Parietal foramina (isolated)                                                           | AD          | 168500  | 5q34–35  | MSX2    | Muscle segment homeobox 2                                             |                                                                      |

See also pycnodysostosis, wrinkly skin syndrome, and several others

33. Craniosynostosis syndromes

| Pfeiffer syndrome (FGFR1-related)                                                      | AD          | 101600  | 8p12     | FGFR1   | Fibroblast growth factor receptor 1                                    | Most have FGFR1 P252R mutation (phenotype generally milder than FGFR2-related Pfeiffer) |
| Pfeiffer syndrome (FGFR2-related)                                                      | AD          | 101600  | 10q26.12 | FGFR2   | Fibroblast growth factor receptor 2                                    | Includes Jackson–Weiss syndrome (MIM 123150) and Antley–Bixler variants caused by FGFR2 mutations (see below) |
| Apert syndrome                                                                         | AD          | 101200  | 10q26.12 | FGFR2   | Fibroblast growth factor receptor 2                                    |                                                                      |
| Craniosynostosis with cutis gyrata (Beare–Stevenson)                                   | AD          | 123790  | 10q26.12 | FGFR2   | Fibroblast growth factor receptor 2                                    |                                                                      |
| Crouzon syndrome                                                                       | AD          | 123500  | 10q26.12 | FGFR2   | Fibroblast growth factor receptor 2                                    |                                                                      |
| Disorder                                                                 | Mode of Inheritance | Chromosome Region | Gene     | Pathological Description                                                                 | Reference ноября |
|-------------------------------------------------------------------------|--------------------|-------------------|----------|----------------------------------------------------------------------------------------|----------------|
| Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome) | AD                 | 4p16.3            | FGFR3    | Defined by specific FGFR3 A391E mutation                                                |                |
| Craniosynostosis, Muenke type                                           | AD                 | 4p16.3            | FGFR3    | Fibroblast growth factor receptor 3 defined by specific FGFR3 P250R mutation           |                |
| Antley–Bixler syndrome                                                 | AR                 | 7q11.23           | POR      | Cytochrome P450 oxidoreductase                                                         |                |
| Craniostenosis Boston type                                             | AD                 | 5q35.2            | MSX2     | Heterozygous P148H mutation in a single family                                           |                |
| Saethre–Chotzen syndrome                                               | AD                 | 7p21.1            | TWIST1   | Some cases reported with FBN1 mutations classified as Pfeiffer syndrome (MIM 207410) |                |
| Shprintzen–Goldberg syndrome                                           | AD                 | 8q22.12           | TWIST    |                                                                                         |                |
| Baller–Gerold syndrome                                                 | AR                 | 8q24.3            | RECOL4   | RECO protein-like 4                                                                     |                |
| Carpenter syndrome                                                     | AR                 | 5q32              | TCOF1    | Treacher Collins-Franceschetti syndrome 1                                              |                |
| Mandibulo-facial dysostosis                                           | AD                 | 5q32              | POLR1D   | Polymerase (RNA) I polypeptide D                                                        |                |
| Mandibulo-facial dysostosis                                           | AD                 | 13q12.2           | POLR1C   | Polymerase (RNA) I polypeptide C                                                        |                |
| Mandibulo-facial dysostosis                                           | AR                 | 6p21.1            | POLR1C   | chr. X open reading frame 5                                                            |                |
| Oral-facial-digital syndrome type I (OFD1)                              | XLR                | Xp22.3            | CXORF5   | Ellis–van Creveld 1 protein                                                             |                |
| Weyer acrofacial (acroental) dysostosis                                | AD                 | 4p16              | EVC1     |                                                        |                |
| Endocrine-cerebro-osteodysplasia (ECO)                                  | AR                 | 6p12.3            | ICK      | Intestinal cell kinase                                                                  |                |
| Craniofrontonasal syndrome                                            | XLD                | Xq13.1            | EFNBI    | Ephrin B1                                                                               |                |
| Frontonasal dysplasia, type 1                                          | AR                 | 1q13.3            | ALX3     | Aristaless-like-3                                                                      |                |
| Frontonasal dysplasia, type 2                                          | AR                 | 11p11.2           | ALX4     | Aristaless-like-4                                                                       |                |
| Frontonasal dysplasia, type 3                                          | AR                 | 12q21.3           | ALX1     | Aristaless-like 1                                                                       |                |
| Hemifacial microsomia                                                  | SP/AD              | 16q21.1           | DHHODH   | Dihydroorotate dehydrogenase                                                           |                |
| Miller syndrome (postaxial acrofacial dysostosis)                      | AR                 | 16q22             | DHHODH   | Dihydroorotate dehydrogenase                                                           |                |
| Acrofacial dysostosis, Nager type                                       | AD/AR              | 15q4400           | HBB      | Homeobox gene HB9                                                                       |                |
| Acrofacial dysostosis, Rodriguez type                                  | AR                 | 20q11.70          | HBB      | HOME Box gene HB9                                                                       |                |

See also Cole–Carpenter syndrome in group 24, CDAGS syndrome in group 29, and Craniofrontonasal syndrome in group 34.

34. Dysostoses with predominant craniofacial involvement

35. Dysostoses with predominant vertebral with and without costal involvement

(Continued)
| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Spondylocostal dysostosis type 2 (SCD2) | AR | 608681 | 15q26 | MESP2 | Mesoderm posterior (expressed in) 2 | |
| Spondylocostal dysostosis type 3 (SCD3) | AR? | 609813 | 7p22 | LFNG | Lunatic fringe | |
| Spondylocostal dysostosis type 4 (SCD4) | AR | 17p13.1 | HES7 | Hairy-and-enhancer-of-split-7 | |
| Spondylothoracic dysostosis | AR | 15q26 | MESP2 | Mesoderm posterior (expressed in) 2 | |
| Klippel–Feil anomaly with laryngeal malformation | AD | 148900 | 8q22.1 | GDF6 | Growth and differentiation factor 6 | Role of GDF6 mutations in dominant spondylothoracic dysostosis unclear See also GDF6, above |
| Spondylocostal/thoracic dysostosis, other forms | AD/AR | | | | |
| Cerebro-costo-mandibular syndrome (rib gap syndrome) | AD/AR | 117650 | | | |
| Cerebro-costo-mandibular-like syndrome with vertebral defects | AD | 611209 | 17q25 | COG1 | Component of oligomeric Golgi complex 1 | Also classified as CDG type IIg |
| Diaphanospondylohydysostosis | AR | 608022 | 7p14 | BMPER | Bone morphogenetic protein-binding endothelial cell precursor-derived regulator | Possibly overlaps withischiospinal dysostosis |

See also Spondylocarpotarsal dysplasia in group 7 and spondylo-metaphyseal-megaepiphysial dysplasia in group 13

36. Patellar dysostoses

| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Ischiopatellar dysplasia (small patella syndrome) | AD | 147891 | 17q21–q22 | TBX4 | T-box gene 4 | |
| Small patella—like syndrome with clubfoot | AD | | 5q31 | PITX1 | Paired-like homeodomain transcription factor 1 (pituitary homeobox 1) | Includes isolated dominant familial clubfoot |
| Nail-patella syndrome | AD | 161200 | 9q34.1 | LMX1B | LIM homeobox transcription factor 1 | |
| Genitopatellar syndrome | AR? | 606170 | | | | |
| Ear-patella-short stature syndrome (Meier-Gorlin) | AR | 224690 | | | | |

See also MED group for conditions with patellar changes as well as ischio-pubic-patellar dysplasia as mild expression of campomelic dysplasia

37. Brachydactylies (with or without extraskeletal manifestations)

| Group/name of disorder | Inheritance | MIM No. | Locus | Gene | Protein | Notes |
|------------------------|-------------|---------|-------|------|---------|-------|
| Brachydactyly type A1 | AD | 112500 | 2q35–36 | IHH | Indian Hedgehog | |
| Brachydactyly type A1 | AD | | 5p31 | | Bone morphogenetic protein receptor, 1B | |
| Brachydactyly type A2 | AD | 112600 | 4q23 | BMPR1B | Bone morphogenetic protein type 2 | |
| Brachydactyly type A2 | AD | | 112600 | BMP2 | Bone morphogenetic protein type 2 | |
| Brachydactyly type A2 | AD | 112600 | 3p11.2 | GDF5 | Growth and differentiation factor 5 | |
| Brachydactyly type A3 | AD | 112700 | | | | |
| Condition                                      | Mode | Chromosome | Gene          | Description                                                                 |
|-----------------------------------------------|------|------------|---------------|-----------------------------------------------------------------------------|
| Brachydactyly type B                          | AD   | 9q22       | ROR2          | Receptor tyrosine kinase-like orphan receptor 2                             |
| Brachydactyly type B2                         | AD   | 17q        | NODG          | Noggin                                                                      |
| Brachydactyly type C                          | AD, AR | 20q11.2    | GDF5          | Growth and differentiation factor 5                                          |
| Brachydactyly type D                          | AD   | 2q31       | HOXD13        | Homeobox D13, Parathyroid hormone-like hormone [parathyroid hormone related peptide, PTHRP] |
| Brachydactyly type E                          | AD   | 2q31       | HDAC4         | Histone deacetylase 4                                                       |
| Brachydactyly—mental retardation syndrome     | AD   | 2q37.3     | HDAC4         | Phosphatidylinositol-glycan biosynthesis class V protein [GPI mannosyltransferase 2] |
| Hyperphosphatasia with mental retardation, brachytelephalangy, and distinct face | AR   | 1p36.11    | PIGV          | Phosphatidylinositol-glycan biosynthesis class V protein [GPI mannosyltransferase 2] |
| Brachydactyly-hypertension syndrome [Bilginturian] | AD   | 12p12.2−11.2 |              | Possibly PTHLH                                                             |
| Brachydactyly with anonychia [Cooks syndrome] | AD   | 17q24.3    | SOX9          | Regulatory mutations                                                         |
| Microcephaly-oculo-digito-esophageal-duodenal syndrome [Feingold syndrome] | AD   | 2p24.1     | MYCN          | nMYC oncogene                                                               |
| Hand-foot-genital syndrome                    | AD   | 7p14.2     | HOXA13        | Homeobox A13                                                                |
| Brachydactyly with elbow dysplasia [Liebenberg syndrome] | AD   | 186550    |              |                                                                           |
| Keutel syndrome                               | AR   | 12p13.1−12.3 | MGP          | Matrix Gla protein                                                           |
| Albright hereditary osteodystrophy [AHO]      | AD   | 20q13      | GNAS1         | Guanine nucleotide binding protein of adenylate cyclase—subunit             |
| Rubinstein–Taybi syndrome                     | AD   | 10p13.3    | CREBBP        | CREB-binding protein                                                        |
| Rubinstein–Taybi syndrome                     | AD   | 16p13.3    | EP300         | E1A-binding protein, 300-kDa                                                |
| Catel–Manzke syndrome                         | XLR? | 302380     |              |                                                                           |
| Brachydactyly, Temtamy type                   | AR   | 605282     |              |                                                                           |
| Christian type brachydactyly                  | AD   | 112450     |              |                                                                           |
| Coffin–Siris syndrome                         | AR   | 135900     |              |                                                                           |
| Mononen type brachydactyly                    | XLD? | 301940     |              |                                                                           |
| Poland anomaly                                | SP   | 173800     |              |                                                                           |

See also group 20 for other conditions with brachydactyly as well as brachytelephalangic CDP

### 38. Limb hypoplasia—reduction defects group

| Condition                                      | Mode | Chromosome | Gene          | Description                                                                 |
|-----------------------------------------------|------|------------|---------------|-----------------------------------------------------------------------------|
| Ulnar-mammary syndrome                        | AD   | 181450     | TBX3          | T-box gene 3                                                                |
| de Lange syndrome                             | AD   | 122470     | NIPBL         | Nipped-B-like                                                               |
| Fanconi anemia [see note below]               | AR   | 227650     | Several       | Several                                                                     |

See also group 20 for other conditions with brachydactyly as well as brachytelephalangic CDP

(Continued)
| Group/name of disorder                          | Inheritance | MIM No. | Locus    | Gene       | Protein                      | Notes                                                                 |
|------------------------------------------------|-------------|---------|----------|------------|------------------------------|----------------------------------------------------------------------|
| Thrombocytopenia-absent radius (TAR)           | AR/AD?      | 274000  | 1q21.1   | Several    |                              |                                                                      |
| Thrombocytopenia with distal limb defects      | AD          |         | 3q27     | THPO       | Thrombopoietin               |                                                                      |
| Holt–Oram syndrome                             | AD          | 142900  | 12q24.1  | TBX5       | T-box gene 5                 |                                                                      |
| Okihiro syndrome (Duane—radial ray anomaly)    | AD          | 607323  | 20q13    | SALL4      | SAL-like 4                   |                                                                      |
| Cousin syndrome                                | AR          | 260660  | 1p13     | TBX15      | T-box gene 15                |                                                                      |
| Roberts syndrome                               | AR          | 268300  | 8p21.1   | ESCO2      | Homolog of establishment of  |                                                                      |
| Split-hand-foot malformation with long bone    | AD          | 119100  | 1q42.2—q43|            |                              |                                                                      |
| defect (SHFLD1)                                |             |         |          |            |                              |                                                                      |
| Split-hand-foot malformation with long bone    | AD          | 610685  | 6q14.1   |            |                              |                                                                      |
| deficiency (SHFLD2)                            |             |         |          |            |                              |                                                                      |
| Split-hand-foot malformation with long bone    | AD          | 612576  | 17p13.1  |            |                              |                                                                      |
| deficiency (SHFLD3)                            |             |         |          |            |                              |                                                                      |
| Tibial hemimelia                               | AR          | 275220  |          |            |                              |                                                                      |
| Tibial hemimelia-polydactyly-triphalangeal     | AD          | 188770  |          |            |                              |                                                                      |
| thumb                                          |             |         |          |            |                              |                                                                      |
| Acheiropodia                                   | AR          | 200500  | 7q36     | LMBr1      | Putative receptor protein    |                                                                      |
| Tetra-amelia                                   | XL          | 301090  | 17q21    | WNT3       | Wingless-type MMTV integration site family, member 3 |                                                                      |
| Tetra-amelia                                   | AR          | 273395  | 3q27     | P63 [TP63] | Tumor protein p63            |                                                                      |
| Ankyloblepharon-ectodermal dysplasia-cleft lip | AD          | 106260  | 3q27     | P63 [TP63] | Tumor protein p63            |                                                                      |
| palate [AEC]                                   |             |         |          |            |                              |                                                                      |
| Ectrodactyly-ectodermal dysplasia clef-         | AD          | 604292  | 3q27     | P63 [TP63] | Tumor protein p63            |                                                                      |
| palate syndrome Type 3 (EEC3)                  |             |         |          |            |                              |                                                                      |
| Ectrodactyly-ectodermal dysplasia clef-palate  | AD          | 129900  | 7q11.2—12.3|            |                              |                                                                      |
| syndrome type 1 (EEC1)                         |             |         |          |            |                              |                                                                      |
| Ectrodactyly-ectodermal dysplasia-macular       | AR          | 225280  | 16q22    | CDH3       | Cadherin 3                   |                                                                      |
| dystrophy syndrome (EEM)                       |             |         |          |            |                              |                                                                      |
| Limb-mammary syndrome (including ADULT syndrome)| AD          | 603273  | 3q27     | P63 [TP63] | Tumor protein p63            |                                                                      |
| Split hand-foot malformation, isolated form,   | AD          | 605289  | 3q27     | P63 [TP63] | Tumor protein p63            |                                                                      |
| type 4 (SHFM4)                                 |             |         |          |            |                              |                                                                      |
| Split hand-foot malformation, isolated form,   | AD          | 183600  | 7q21.3—22.1|            |                              |                                                                      |
| type 1 (SHFM1)                                 |             |         |          |            |                              |                                                                      |
| Split hand-foot Malformation, isolated form,   | XL          | 313350  | Xq26     |            |                              |                                                                      |
| type 2 (SHFM2)                                 |             |         |          |            |                              |                                                                      |
| Split hand-foot malformation, isolated form,   | AD          | 600095  | 10q24    | FBXW4      | Dactylin                     |                                                                      |
| type 3 (SHFM3)                                 |             |         |          |            |                              |                                                                      |
| Split hand-foot malformation, isolated form,   | AD          | 606708  | 2q31     |            |                              |                                                                      |
| Condition                                                                 | Code    | Chromosome | Gene       | Description                                                                 |
|--------------------------------------------------------------------------|---------|------------|------------|-----------------------------------------------------------------------------|
| Al-Awadi Raas–Rothschild limb-pelvis hypoplasia–aplasia                  | AR      | 3p25       | WNT7A      | Wingless-type MMTV integration site family, member 7A                      |
| Fuhrmann syndrome                                                        | AR      | 3p25       | WNT7A      | Wingless-type MMTV integration site family, member 7A                      |
| RAPADILOINO syndrome                                                     | AR      | 3p25       | RECQL4     | RECO protein-like 4                                                        |
| Adams–Oliver syndrome                                                    | AD/AR   | 3p25       |            | Some phenotypic overlap with FFU syndrome (below)                          |
| Femoral hypoplasia-unusual face syndrome [FHUFS]                         | SP/AD?  | 3p25       |            |                                                                            |
| Femur-fibula-ulna syndrome [FFU]                                         | SP?     | 3p25       |            |                                                                            |
| Hanhart syndrome                                                         | AD      | 3p25       |            |                                                                            |
| (hypoglossia–hypodactyly)                                                | AD      | 3p25       |            |                                                                            |
| Scapulo-iliac dysplasia [Kosenow]                                        | AD      | 3p25       |            |                                                                            |
| Note: the particularly complex genetic basis of Fanconi anemia and its complementation groups are acknowledged but not further listed in this Nosology. The Reader is referred to MIM or to specialized reviews. See also CHILD in group 20 and the mesomelic and acromesomelic dysplasias |

### 39. Polysyntlyy—Syndactyly—Triphalangism group

| Condition                                                                 | Code    | Chromosome | Gene       | Description                                                                 |
|--------------------------------------------------------------------------|---------|------------|------------|-----------------------------------------------------------------------------|
| Preaxial polydactyly type 1 (PPD1)                                        | AD      | 7q36       | SHH        | Sonic Hedgehog                                                            |
| Preaxial polydactyly type 1 (PPD1)                                        | AD      | 7q36       | SHH        | Sonic Hedgehog                                                            |
| Preaxial polydactyly type 2 (PPD2)/triphalangeal thumb [TPT]              | AD      | 7q36       | SHH        | Sonic Hedgehog                                                            |
| Preaxial polydactyly type 3 (PPD3)                                        | AD      | 7q36       | GLI3       | Gli-Kruppel family member 3                                               |
| Preaxial polydactyly type 4 (PPD4)                                        | AD      | 7q36       | GLI3       | Gli-Kruppel family member 3                                               |
| Greig cephalopolysyndactyly syndrome                                     | AD      | 7q36       | GLI3       | Gli-Kruppel family member 3                                               |
| Pallister–Hall syndrome                                                   | AD      | 7q36       | GLI3       | Gli-Kruppel family member 3                                               |
| Synpolydactyly (complex, fibulin1—associated)                            | AD      | 22q13.3    | FBLN1      | Fibulin 1                                                                  |
| Synpolydactyly                                                           | AD      | 2q31       | HOXD13     | Homeobox D13                                                               |
| Townes–Brock syndrome (Renal-Ear-Anal-Radial syndrome)                   | AD      | 16q12.1    | SALL1      | SAL-like 1                                                                 |
| Lacrimo-auriculo-dento-digital syndrome [LADD]                            | AD      | 5p13–p12   | FGFR3      | Fibroblast growth factor receptor 3                                        |
| Lacrimo-auriculo-dento-digital syndrome [LADD]                            | AD      | 5p13–p12   | FGFR3      | Fibroblast growth factor receptor 3                                        |
| Acrocallosal syndrome                                                     | AD      | 5p13–p12   | FGFR3      | Fibroblast growth factor receptor 3                                        |
| Acro-pectoral syndrome                                                   | AD      | 7q36       | FGFR3      | Fibroblast growth factor receptor 3                                        |
| Acro-pectoro-vertebral dysplasia [F-syndrome]                            | AD      | 7q36       | FGFR3      | Fibroblast growth factor receptor 3                                        |
| Mirror-image polydactyly of hands and feet (Laurin–Sandrow syndrome)    | AD      | 7q36       | SHH        | Sonic Hedgehog                                                            |
| Mirror-image polydactyly of hands and feet (Laurin–Sandrow syndrome)     | AD      | 7q36       | SHH        | Sonic Hedgehog                                                            |
| Cenani–Lenz syndactyly                                                    | AR      | 11p11.2    | LRP4       | Low density lipoprotein receptor-related protein 4                         |
| Group/name of disorder                                      | Inheritance | MIM No.   | Locus     | Gene        | Protein                | Notes                                                                 |
|----------------------------------------------------------|-------------|-----------|-----------|-------------|------------------------|----------------------------------------------------------------------|
| Cenani–Lenz like syndactyly                             | SP (AD?)    |           | 15q13–q14| GREM1, FMN1 | Gremlin 1, Formin 1    | Monoallelic duplication of both loci (observed in one case only so far)|
| Oligosyndactyly, radio-ulnar synostosis, hearing loss, and renal defects syndrome | SP (AR?)    |           | 15q13–q14| FMN1        | Formin 1               | Deletion                                                              |
| Syndactyly, Malik–Percin type                          | AD          | 609432    | 17p13.3   | FAM58A      |                        |                                                                      |
| STAR syndrome (syndactyly of toes, telecanthus, ano-, and renal malformations) | AD          | 300767    | Xq28      |             |                        |                                                                      |
| Syndactyly type 1 (III–IV)                              | AD          | 185900    | 2q34–36   | GJA1        |                        |                                                                      |
| Syndactyly type 3 (IV–V)                                | AD          | 185900    | 6q21–23   | SHH         | Sonic Hedgehog        |                                                                      |
| Syndactyly type 4 (I–V) Haas type                       | AD          | 186200    | 7q36      | SHH         |                        |                                                                      |
| Syndactyly type 5 (syndactyly with metacarpal and metatarsal fusion) | AD          | 186300    | 2q31      | HOXD13      |                        |                                                                      |
| Syndactyly with craniosynostosis                         | AD          | 601222    | 2q35–36.3 |             |                        |                                                                      |
| Syndactyly with microcephaly and mental retardation     | AR          | 272440    |           |             |                        |                                                                      |
| Meckel syndrome type 1                                   | AR          | 249000    | 17q23     | MKS1        |                        |                                                                      |
| Meckel syndrome type 2                                   | AR          | 603194    | 11q       |             |                        |                                                                      |
| Meckel syndrome type 3                                   | AR          | 607361    | 8q21      | TMEM67      |                        |                                                                      |
| Meckel syndrome type 4                                   | AR          | 611134    | 12q       | CEP290      |                        |                                                                      |
| Meckel syndrome type 5                                   | AR          | 611561    | 16q12.1   | RGRPII1L    |                        |                                                                      |
| Meckel syndrome type 6                                   | AR          | 612284    | 4p15      | CC2D2A      |                        |                                                                      |

**Note:** the Smith–Lemli–Opitz syndrome can present with polydactyly and/or syndactyly. See also the SRPS group

### 40. Defects in joint formation and synostoses

| Multiple synostoses syndrome type 1                      | AD          | 186500    | 17q22     | NOD         | Noggin                 | Growth and differentiation factor 5                                    |
|----------------------------------------------------------|-------------|-----------|-----------|-------------|------------------------|----------------------------------------------------------------------|
| Multiple synostoses syndrome type 2                      | AD          | 186500    | 20q11.2   | GDF5        |                        |                                                                      |
| Multiple synostoses syndrome type 3                      | AD          | 612961    | 13q11–q12 | FGF9        |                        |                                                                      |
| Proximal symphalangism type 1                            | AD          | 185800    | 17q22     | NOD         | Noggin                 | Growth and differentiation factor 5                                    |
| Proximal symphalangism type 2                            | AD          | 185800    | 20q11.2   | GDF5        |                        |                                                                      |
| Radio-ulnar synostosis with amegakaryocytic thrombocytopenia | AD          | 605432    | 7p15–14.2 | HOXA11      | Homeobox A11           |                                                                      |

*See also Spondylo-Carpal-Tarsal dysplasia; mesomelic dysplasia with acral synostoses; and others*
each gene separately, advocated by some scholars, is more confusing than helpful in clinical practice.

Group 26 has seen the identification of several novel molecular mechanisms leading to hypophosphatemic rickets.

In Group 29 (Disorganized Development of Skeletal Components), neurofibromatosis type 1 has been included following the points made by Stevenson and others that although the main clinical features of NF1 are neurologic and cutaneous, the skeletal features are frequent, diagnostically helpful and clinically relevant [Stevenson et al., 2007].

Groups 30 (Overgrowth syndromes with significant skeletal involvement) and Group 31 (Genetic inflammatory/rheumatoid-like osteoarthropathies) have been newly added. Group 30 comprises disorders that present as overgrowth syndromes and have a significant skeletal component that is part of the diagnostic criteria for a specific condition. One condition has been tentatively included because of its conspicuous skeletal features [Nishimura et al., 2004; Schmidt et al., 2007]; however this condition remains incompletely delineated. Group 31 includes disorders with features of inflammation and skeletal involvement. The creation of these two groups has been suggested by the frequent diagnostic overlap between these disorders and primary skeletal disorders as well as by the identification of the genetic basis of such disorders in recent years, allowing for a more precise delineation of the phenotypes.

Finally, groups 32–40 are dedicated to the dysostoses and follow again anatomical criteria (cranium, face, axial skeleton, extremities) with additional criteria reflecting principles of embryonic development such as limb reduction or hypoplasia (proximal-distal growth) versus terminal differentiation and patterning of the digits or joint formation. These groups have seen a marked increase in conditions with identified molecular bases and there are indications of a much larger heterogeneity yet.

A single group, the Brachyolmias (formerly group 13), has been deleted. Following the inclusion of dominant brachyolmia in the TRP4 group, the few remaining short-trunk disorders have been incorporated in the SED group.

**DISCUSSION**

**Why “Groups”?**

The assignment of individual disorders into groups has been practiced since the first versions of the “Nomenclature.” At that time, with little biochemical or molecular information available, the grouping of disorders reflected the belief that disorders with similar phenotypic features (e.g., *dysostosis multiplex*) might be caused by disturbances in related metabolic pathways or gene networks (in the case of dysostosis multiplex, lysosomal degradation). This notion has been confirmed by the identification of biochemically related groups, such as those of mineralization disorders or lysosomal disorders, and of genetic families such as the collagen 2 family, the FGFR3 family, and the DTDST family. The grouping of disorders is necessary because of the sheer number of conditions included, and can be helpful in making a differential diagnosis based on the main phenotypic findings, for example, in the mesomelic dysplasias or in chondrodysplasia punctata. Some groups are still defined by common radiographic features or by anatomical site involved. Moreover, the nosology committee recognizes that some readers may disagree with our placement of a clinical entity into one group, when it may fit equally well in another group.

**Which Classification Criteria to Use?**

Criticism to the previous versions of the Nosology has focused on its “hybrid” nature, in the sense that it does not stick to a single systematic approach, be it clinical or molecular. This hybrid nature is intrinsic to the process of unraveling the underlying bases of skeletal diseases; disorders are classified on phenotypic similarities first, and as their molecular bases become understood they may be reclassified based on the gene or pathway that is abnormal. The first aim of the Nosology is to provide a reference list, and only secondarily to help in the diagnostic process. It must therefore coexist with other classifications that are based either on the clinical and radiographic approach to diagnosis, or on the affected molecular systems and pathways. As more and more resources are published on the World Wide Web, crosslinking between classifications and databases may facilitate their simultaneous use.

Although care has been given to apply the inclusion criteria uniformly, there are disorders without proven molecular or biochemical defect for which inclusion in the Nosology as distinct entities seem somewhat arbitrary. For these disorders, discussion within the Nosology group, where individual opinions can be harmonized and, if needed, corrected by the collective expertise, is of great importance. Moreover, there are disorders listed in MIM that have not met our inclusion criteria, in most instances because of too few observations or because of the lack of features allowing clear diagnostic distinction from other disorders. It is likely that additional observations or the demonstration of a distinct molecular basis will allow for the inclusion of many of these disorders in the future, either as separate entities or as “variants” of already existing ones.

**Dysplasias Versus Dysostoses**

Dysostoses are disorders affecting individual bones or group of bones. In contrast to the “dysplasias,” that arise frequently from defects in structural proteins, metabolic processes or in growth plate regulation, the dysostoses often arise from embryonic morphogenic defects and are thus more closely related to multiple malformation syndromes. Since the first inclusion of dysostoses in the 2001 revision, the number of “dysostoses” included in the Nosology has grown significantly. The present revision includes an even larger number of dysostoses reflecting the advances made in identifying their molecular basis. The boundaries between skeletal dysplasias and dysostoses, metabolic and molecular disorders, and multiple congenital anomalies syndromes is becoming progressively less sharp, and the diagnostic process requires knowledge that crosses between these subspecialty areas; the group of (cranio-)frontonasal disorders and the Franck–ter Haar syndrome can be cited as examples. The MIM catalogue contains many more entries, such as multiple malformation syndromes, that have some degree of skeletal involvement. Emphasis has been given to syndromes in which the skeletal component is prominent and/or essential to the diagnosis.
OMIM and the Nosology

Because of the importance of consistency between parallel databases, the relationship between the Nosology and the OMIM database has been reviewed. The more comprehensive nature of the data collection and filing in OMIM and the different nature of its revision process can lead to a divergence between the inclusion of nosologic entities and their denomination. Thus, OMIM is in general more appositional, while the Nosology tries to do some “housekeeping” of entities by regrouping them and by eliminating those that have been incorporated into others. Efforts to make to harmonize the MIM and the Nosology are underway.

Outlook

The increasing availability of massive parallel sequencing and other new sequencing technologies will likely result in a rapid identification of novel disease-causing genes, but also in novel phenotypes associated with mutations in genes already linked to other phenotypes. In the near future, the catalog of skeletal phenotypes with a genetic basis may become so large as to surpass the scope of a “Nosology” as we understand it presently, and the Nosology will transform into an annotated database.

Even in that case, the many revisions of the Nosology will hopefully have paved the way by setting standards for the recognition and definition of skeletal phenotypes. Past versions of the Nosology have been translated in different languages and have found their way into textbooks of pediatrics and genetics. At present, the Nosology may help the clinician who is struggling for a diagnosis, by providing a simple listing of disorders grouped by cardinal features. The Nosology offers a quick reminder of the many differential diagnoses for one given disorder. As an expert-reviewed list of currently recognized disorders, the Nosology also constitutes a standard against which a possible “new” disorder should be compared. Finally, the Nosology offers a catalogue of genes involved in skeletal development and homeostasis that will be of interest and of inspiration to all those who are working in skeletal biology and medicine.

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