Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision

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The purpose of the nosology is to serve as a “master” list of the genetic disorders of the skeleton to facilitate diagnosis and to help delineate variant or newly recognized conditions. This is the 9th edition of the nosology and in comparison with its predecessor there are fewer conditions but many new genes. In previous editions, diagnoses that were phenotypically indistinguishable but genetically heterogenous were listed separately but we felt this was an unnecessary distinction. Thus the overall number of disorders has decreased from 456 to 436 but the number of groups has increased to 42 and the number of genes to 364. The nosology may become increasingly important today and tomorrow in the era of big data when the question for the geneticist is often whether a mutation identified by next generation sequencing technology in a particular gene can explain the clinical and radiological phenotype of their patient. This can be particularly difficult to answer conclusively in the prenatal setting. Personalized medicine emphasizes the importance of tailoring diagnosis and therapy to the individual but for our patients with rare skeletal disorders, the importance of tapping into a resource where genetic data can be centralized and made

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available should not be forgotten or underestimated. The nosology can also serve as a reference for the creation of locus-specific databases that are expected to help in delineating genotype-phenotype correlations and to harbor the information that will be gained by combining clinical observations and next generation sequencing results. © 2015 Wiley Periodicals, Inc.

**Key words:** skeletal dysplasias; nosology; molecular basis of disease; dwarfism

## INTRODUCTION

The publication of a nosology of skeletal dysplasias started 45 years ago in Paris and has seen multiple revisions [1970, 1971a,b, 1979, 1983, 1998; Hall, 2002; Lachman, 1998; McKusick and Scoot, 1971; Rimoin, 1979; Spranger, 1992; Superti-Furga and Unger, 2007; Warman et al., 2011] The current nosology revision took place in Bologna, Italy just prior to the 11th International Skeletal Dysplasia Society meeting organized by Professor Luca Sangiorgi. In the 2015 version of the nosology, the number of conditions has decreased while the number of genes has increased dramatically. This is a reflection of consolidation of repeat entries into a single one when there is no discernible phenotypic difference while at the same time acknowledging the discovery of new genes. The inclusion of MIM numbers is maintained as this invaluable database is often a first reference for clinicians. There is not a complete concordance between MIM and the nosology because of different inclusion and review criteria and thus MIM retains some obsolete diagnoses and duplicates others (under differing names or eponyms).

This version of the nosology is the 9th edition and while it contains several new disorders, it is not radically different from its predecessor [Warman et al., 2011]. The groups of disorders remain a hybrid mix as they are defined either by a single gene or group of related genes (e.g., FGF3 chondrodysplasia group and sulphation disorders group), or by a particular phenotypic feature (e.g., dysplasias with multiple joint dislocations), or by some radiological finding (e.g., metaphyseal dysplasia group and slender bone dysplasia group).

When the concept of the skeletal dysplasia families was first elaborated, it was hoped that there would be a limited number of molecular based groups with each group containing multiple allelic disorders [Spranger, 1985]. However, the biology of the skeletal dysplasias has turned out to be much richer, and more complex than anticipated. So while it makes sense to have a type 2 collagen disorder group where there is some similarity between conditions but enough phenotypic difference to warrant separate diagnoses (e.g., Stickler syndrome versus achondrogenesis type 2), there are many other genes that, to the best of our knowledge, are not associated with a “skeletal dysplasia family,” those with no wide spectrum (e.g., SEDL (Spondyloepiphyseal dysplasia tarda) or Spondyloepimetaphyseal dysplasia with joint laxity-leptodactylic type). For these genes and conditions, it still makes sense to group them with clinically or radiographically similar disorders.

Table I has been simplified with the columns “locus” and “gene” merged into one. For some disorders, the etiology is a copy number disturbance and thus they are not single gene disorders in the classic sense. For those disorders with a known causative gene, the chromosomal location of that gene is often not important (especially if it is an autosome), and when necessary, the information can be readily retrieved from public databases.

The criteria used for inclusion of disorders are unchanged from the previous revision [Warman et al., 2011]. They are:

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 (observations, even those by experts in the field should not find their way into the nosology before they have achieved peer-reviewed status).
3. Genetic basis proven by pedigree or very likely based on homogeneity of phenotype in unrelated families.
4. Nosologic autonomy confirmed by experimental analysis.

We have included conditions in which only one family has been described but for which the gene has been identified. For e.g., the heterozygous mutations in FZD2 in dominant omodysplasia [Saal et al., 2015].

The total number of diseases has gone down (from 456 to 436) thanks to grouping of phenotypically indistinguishable entities and despite the appearance of several new conditions (e.g., MAGMAS related skeletal dysplasia) [Mehawej et al., 2014].

A few groups have changed names in this edition and the overall number has increased from 40 to 42. The short-rib dysplasia (with or without polydactyly) group has become the ciliopathies with major skeletal involvement group. Due to the increasing number and complexity of the brachydactylies, the group has now been made into two separate categories: brachydactylies without extra-skeletal manifestations and brachydactylies with extraskletal manifestations. The ectrodactylies have been given their own group.

The field of osteogenesis imperfecta (OI) continues to expand with multiple new genes. We have chosen to stick with the Silence classification that was phenotypically and not molecularly based [Silence and Rimoin, 1978; Silence et al., 1979]. For this reason, OI type 5 is included as it is radiologically distinguishable from types 1 through 4. OI is the archetype of a skeletal dysplasia for which molecular diagnosis relies on next generation sequencing but prognosis is based on the careful phenotypic observations collected over the last four decades [Van Dijk and Silence, 2014]. Examples are also available from other domains of medical genetics (spino–cerebellar ataxia or Meckel–Gruber syndrome).

## DISCUSSION

The pace of disease related gene discovery has accelerated phenomenally in recent years thanks to the development of next-generation sequencing technologies and increasing availability of whole exome sequencing. This has led to both expansion and contraction of the nosology. It has expanded to incorporate new genes and new conditions but also contracted as we recognize our limits in differentiating by phenotype. While each patient may be unique, there are clear advantages both medical and human to belonging to a group of similar individuals [Superti-Furga, 2014]. It is truly an exciting time as we struggle to correctly interpret the
| Group/Name of Disorder                                      | Inheritance | MIM No. | Locus or Gene | Protein | Notes                                                                 |
|------------------------------------------------------------|-------------|---------|---------------|---------|----------------------------------------------------------------------|
| **1. FGFR3 chondrodysplasia group**                        |             |         |               |         |                                                                      |
| Thanatophoric dysplasia type 1 [TD1]                      | AD          | 187600  | FGFR3         | FGFR3   | Includes previous San Diego type                                     |
| Thanatophoric dysplasia type 2 [TD2]                      | AD          | 187601  | FGFR3         | FGFR3   |                                                                      |
| Severe achondroplasia with developmental delay and acanthosis nigricans [SADDAN] | AD          | 187600  | FGFR3         | FGFR3   |                                                                      |
| Achondroplasia                                             | AD          | 100800  | FGFR3         | FGFR3   |                                                                      |
| Hypochondroplasia                                          | AD          | 146000  | FGFR3         | FGFR3   |                                                                      |
| Camptodactyly, tall stature and hearing loss syndrome [CATSHL] | AD          | 610474  | FGFR3         | FGFR3   | Inactivating mutation                                                 |
| Hypochondroplasia–like dysplasia[s]                       | AD, SP      |         |               |         |                                                                      |

See also group 33 for craniosynostoses syndromes linked to FGFR3 mutations, as well as LADD syndrome in group 41 for another FGFR3-related phenotype.

| **2. Type 2 collagen group**                                |             |         |               |         |                                                                      |
|------------------------------------------------------------|-------------|---------|---------------|---------|----------------------------------------------------------------------|
| Achondrogenesis type 2 [ACG2; Langer-Saldino]              | AD          | 200610  | COL2A1       | Type 2 collagen |                                                                      |
| Platyspondyl dysplasia, Torrance type                      | AD          | 151210  | COL2A1       | Type 2 collagen | See also Severe Spondylo dysplastic dysplasias [group 14]           |
| Hypochondrogenesis                                         | AD          | 200610  | COL2A1       | Type 2 collagen |                                                                      |
| Spondyloepiphyseal dysplasia congenital [SEDC]             | AD          | 183900  | COL2A1       | Type 2 collagen |                                                                      |
| Spondyloepimaphyseal dysplasia [SEMD] Strudwick type       | AD          | 184250  | COL2A1       | Type 2 collagen | Includes previous SMD Algerian type, Dys spondyloenchondromatosis and former SMD with severe genu valgum |
| Kniest dysplasia                                            | AD          | 156550  | COL2A1       | Type 2 collagen |                                                                      |
| Spondyloepimaphyseal dysplasia                              | AD          | 271700  | COL2A1       | Type 2 collagen |                                                                      |
| Mild SED with premature onset arthrosis                    | AD          | 277550  | COL2A1       | Type 2 collagen |                                                                      |
| SED with metatarsal shortening (formerly Czech dysplasia)  | AD          | 609162  | COL2A1       | Type 2 collagen |                                                                      |
| Stickler syndrome type 1                                   | AD          | 108300  | COL2A1       | Type 2 collagen |                                                                      |

See also COL11A1, COL11A2, and COL9A1.

| **3. Type 11 collagen group**                               |             |         |               |         |                                                                      |
|------------------------------------------------------------|-------------|---------|---------------|---------|----------------------------------------------------------------------|
| Stickler syndrome type 2                                    | AD          | 604841  | COL11A1      | Type 11 collagen alpha-1 chain |                                                                      |
| Marshall syndrome                                            | AD          | 154780  | COL11A1      | Type 11 collagen alpha-1 chain |                                                                      |
| Stickler syndrome type 3 [non-ocular]                      | AD          | 184840  | COL11A2      | Type 11 collagen alpha-2 chain |                                                                      |
| Fibrochondrogenesis                                         | AR          | 228520  | COL11A1, COL11A2 | Type 11 collagen alpha-1 chain, Type 11 collagen alpha-2 chain |
| AR, AD                                                     | 614524     | COL11A2 | Type 11 collagen alpha-2 chain |                                                                      |
| Oto-spondylo-mega-epiphyseal dysplasia (OSMED), recessive type | AR          | 215150  | COL11A2      | Type 11 collagen alpha-2 chain |                                                                      |
| Oto-spondylo-mega-epiphyseal dysplasia (OSMED), dominant type [Weissenbacher–Zweymüller syndrome, Stickler syndrome type 3] | AD          | 277610  | COL11A2      | Type 11 collagen alpha-2 chain |                                                                      |

See also Stickler syndrome type 1 in group 2.

(Continued)
| Group/Name of Disorder | Inheritance | MIM No. | Locus or Gene | Protein | Notes |
|-----------------------|-------------|---------|---------------|---------|-------|
| 4. Sulphation disorders group | | | | | |
| Achondrogenesis type 1B (ACG1B) | AR | 600972 | DTDS | SLC26A2 sulfate transporter | Formerly known as Fraccaro type achondrogenesis |
| Atelosteogenesis type 2 (AO2) | AR | 256050 | DTDS | SLC26A2 sulfate transporter | Includes de la Chapelle dysplasia, McAlister dysplasia, and “neonatal osseous dysplasia” |
| Diastrophic dysplasia (DTD) | AR | 222600 | DTDS | SLC26A2 sulfate transporter | See also multiple epiphyseal dysplasias and pseudoachondroplasia group (group 9) |
| MED, autosomal recessive type (rMED; EDM4) | AR | 226900 | DTDS | SLC26A2 sulfate transporter | See also multiple epiphyseal dysplasias and pseudoachondroplasia group (group 9) |
| SEMD, PAPSS2 type | AR | 612847 | PAPSS2 | PAPS-Synthetase 2 | Formerly “Pakistani type”. See also SEMD group (group 13) |
| Brachyolmia, recessive type | AR | 612847 | PAPSS2 | PAPS-Synthetase 2 | Probably includes Toledo and Hobaek types of brachyolmia |
| Chondrodysplasia gPAPP type (includes Catel–Manzke-like syndrome) | AR | 614078 | IMPAD1 | Golgi 3-prime phosphoadenosine 5-prime phosphate 3-prime phosphatase | Includes recessive Larsen syndrome, Humero–Spinal Dysostosis, and SEMD Omani type |
| Chondrodysplasia with congenital joint dislocations, CHST3 type (recessive Larsen syndrome) | AR | 608637 | CHST3 | Carbohydrate sulfotransferase 3; chondroitin 6-sulfotransferase | Includes recessive Larsen syndrome, Humero–Spinal Dysostosis, and SEMD Omani type |
| Ehlers–Danlos syndrome, CHST14 type (“musculo-skeletal variant”) | AR | 601776 | CHST14 | Carbohydrate sulfotransferase 14; dermatan 4-sulfotransferase | Includes Adducted Thumb–Clubfoot syndrome |
| 5. Perlecan group | | | | | |
| Dyssegmental dysplasia, Silverman–Handmaker type | AR | 224410 | PLC [HSFG2] | Perlecan | Includes mild and severe forms; includes previous Burton dysplasia |
| Dyssegmental dysplasia, Rolland–Desbuquois type | AR | 224400 | PLC [HSFG2] | Perlecan | Includes mild and severe forms; includes previous Burton dysplasia |
| Schwartz–Jampel syndrome (myotonic chondrodystrophy) | AR | 255800 | PLC [HSFG2] | Perlecan | Includes mild and severe forms; includes previous Burton dysplasia |
| 6. Aggrecan group | | | | | |
| SED, Kimberley type | AD | 608361 | AGC1 | Aggrecan | Some cases apparently lack FLNA mutations |
| SEMD, Aggrecan type | AR | 612813 | AGC1 | Aggrecan | Some cases apparently lack FLNA mutations |
| Familial osteochondritis dissecans | AD | 165800 | AGC1 | Aggrecan | Some cases apparently lack FLNA mutations |
| 7. Filamin group and related disorders | | | | | |
| Frontometaphyseal dysplasia | XLD | 305620 | FLNA | Filamin A | Some cases apparently lack FLNA mutations |
| Osteodysplasty Melnick–Needles | XLD | 309350 | FLNA | Filamin A | Some cases apparently lack FLNA mutations |
| Otopalatodigital syndrome type 1 (OPD1) | XLD | 311300 | FLNA | Filamin A | Some cases apparently lack FLNA mutations |
| Otopalatodigital syndrome type 2 (OPD2) | XLD | 304120 | FLNA | Filamin A | Some cases apparently lack FLNA mutations |
| Terminal osseous dysplasia with pigmentary defects (TODPD) | XLD | 300244 | FLNA | Filamin A | Some cases apparently lack FLNA mutations |
| Atelosteogenesis type 1 (AO1) | AD | 108720 | FLNB | Filamin B | Includes Boomerang dysplasia, Repkorn dysplasia, and spondylohumeral (giant cell) dysplasia |
| Condition                                      | Mode of Inheritance | Gene       | Description                                                                 |
|-----------------------------------------------|---------------------|------------|-----------------------------------------------------------------------------|
| Atelosteogenesis type 3 (A03)                 | AD                  | FLNB       | Filamin B                                                                   |
| Larsen syndrome (dominant)                    | AD                  | FLNB       | Filamin B                                                                   |
| Spondylo-carpal-tarsal dysplasia              | AR                  | FLNB       | Filamin B                                                                   |
| Frank-ter Haar syndrome                       | AR                  | SH3PXD2B   | TKS4                                                                        |
| Some cases unlinked to FLNB                    |                     |            |                                                                             |
| **8. TRPV4 group**                            |                     |            |                                                                             |
| Metatropic dysplasia                          | AD                  | TRPV4      | Transient receptor potential cation channel, subfamily V, member 4          |
| Includes "hyperplastic", lethal and non-lethal forms |                     |            |                                                                             |
| Spondyloepimetaephyseal dysplasia, Maroteaux type 2 | AD          | TRPV4      | Transient receptor potential cation channel, subfamily V, member 4          |
| (Pseudo-Morquio syndrome type 2)              |                     |            | Includes Parastremmatic [MIM 168400]                                       |
| Spondylometaphyseal dysplasia, Kozlowski type  | AD                  | TRPV4      | Transient receptor potential cation channel, subfamily V, member 4          |
| Brachyolmia, autosomal dominant type           | AD                  | TRPV4      | Transient receptor potential cation channel, subfamily V, member 4          |
| Familial digital arthropathy with brachydactyly | AD                  | TRPV4      | Transient receptor potential cation channel, subfamily V, member 4          |
| **9. Ciliopathies with major skeletal involvement** |                     |            |                                                                             |
| Chondroectodermal dysplasia (Ellis-van Creveld) | AR                  | EVC1       | EvC gene 1                                                                  |
|                                                                                               | EVC2       | EvC gene 2                                                                  |
| Short rib–polydactyly syndrome (SRPS) type 1/3 | AR                  | DYNC2H1    | Dynein, cytoplasmic 2, heavy chain 1                                        |
| (Saldino–Noonan/Verma–Naumoff)                |                     | IFT80      | intraflagellar transport 80 (homolog of)                                    |
|                                                                                               | WDR34      | WD repeat-containing protein 34                                             |
|                                                                                               | DYNC2H1    | Dynein, cytoplasmic 2, heavy chain 1                                        |
|                                                                                               | IFT80      | intraflagellar transport 80 (homolog of)                                    |
|                                                                                               | WDR34      | WD repeat-containing protein 34                                             |
|                                                                                               | TTC21B     | Tetratricopeptide repeat domain-containing protein 21B                     |
|                                                                                               | WDR19      | WD repeat-containing protein 19                                             |
|                                                                                               | IFT172     | intraflagellar transport 172                                               |
|                                                                                               | IFT140     | intraflagellar transport 140                                               |
|                                                                                               | DYNC2H1    | Dynein, cytoplasmic 2, heavy chain 1                                        |
|                                                                                               | NEK1       | Never in mitosis gene a-related kinase 1                                    |
| SRPS type 4 (Beemer)                          | AR                  | WDR35      | WD repeat-containing protein 19                                             |
| SRPS type 5                                  | AR                  | WDR35      | WD repeat-containing protein 19                                             |
| Oral-facial-digital syndrome type 4 (Mohr–Majewski) | AR            | TCTN3      | Tectonic family, member 3                                                  |

(Continued)
| Group/Name of Disorder                                      | Inheritance | MIM No. 1 | Locus or Gene | Protein                      | Notes                                                                 |
|------------------------------------------------------------|-------------|-----------|---------------|------------------------------|----------------------------------------------------------------------|
| Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1, 2 | AR          | 218330    | IFT122        | Intraflagellar transport 122 |                                                                      |
|                                                           |             | 613610    | WDR35         | WD repeat-containing protein 35 |                                                                      |
|                                                           |             | 614099    | WDR19         | WD repeat-containing protein 19 |                                                                      |
|                                                           |             |           | IFT43         | Intraflagellar transport 43  |                                                                      |
| Thoracoaryngopelvic dysplasia (Barnes)                     | AD          | 187760    |               |                              |                                                                      |
|                                                           |             |           |               |                              | See also paternal UPD14 and cerebro-costo-mandibular syndrome         |
| 10. Multiple epiphyseal dysplasia and pseudoachondroplasia group |            |           |               |                              |                                                                      |
| Pseudoachondroplasia (PSACH)                               | AD          | 177170    | COMP          | COMP                         |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 1 (EDM1)          | AD          | 132400    | COL9A2        | Collagen 9 alpha-2 chain      |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 2 (EDM2)          | AD          | 600204    | COL9A3        | Collagen 9 alpha-3 chain      |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 3 (EDM3)          | AD          | 600969    |              |                              |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 5 (EDM5)          | AD          | 607078    | MATH3         | Matrilin 3                   |                                                                      |
| Multiple epiphyseal dysplasia (MED) type 6 (EDM6)          | AD          | 120210    | 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    | COL9A1        | Collagen 9 alpha-1 chain      |                                                                      |
| Familial hip dysplasia (Beukes)                            | AD          | 142669    | 4q35          |                              |                                                                      |
| Multiple epiphyseal dysplasia with microcephaly and nystagmus (Lowry–Wood) | AR          | 226960    |               |                              |                                                                      |
| See also Multiple Epiphyseal Dysplasia, recessive type     |             |           |               |                              |                                                                      |
| [rMED; EDM4] in sulphation 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    | COL10A1       | Collagen 10 alpha-1 chain     |                                                                      |
| Cartilage-hair hypoplasia (CHH; metaphyseal dysplasia, McKusick type) | AD          | 250250    | RMRP          | RNA component of RNase H     | Includes anauxetic dysplasia                                         |
| Metaphyseal dysplasia, CHH-like, POP1 type                 | AR          | 156400    | POP1          | Processing of precursor RNA  | Activating mutations-see also Blomstrand dysplasia [group 23]        |
| Metaphyseal dysplasia, Jansen type                         | AD          | 600002    | PTHR1         | PTH/PTHrP receptor 1          | Activating mutations-see also Blomstrand dysplasia [group 23]        |
| Eiken dysplasia                                            |             |           |               |                              |                                                                      |
| Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Swachman–Bodian–Diamond syndrome, SBDS) | AR          | 260400    | SBDS          | SBDS protein                 |                                                                      |
| Metaphyseal anadysplasia type 1                            | AD, AR      | 602111    | MMP13         | Matrix metalloproteinase 13  | Includes SEMD Missouri type.                                         |
| Metaphyseal anadysplasia type 2                            | AR          | 613073    | MMP9          | Matrix metalloproteinase 9   |                                                                      |
| Metaphyseal anadysplasia, Spahr type                       | AR          | 250400    | MMP13         | Matrix metalloproteinase 13  | Includes autosomal recessive anadysplasia                           |
| Metaphyseal dysplasia with maxillary hypoplasia            | AD          | 156510    | RUNX2         | Runt-related transcription factor 2 |                                                                      |
| 12. Spondylometaphyseal dysplasias (SMD)                   | AR          | 271550    | ACP5          | Tartrate-resistant acid phosphatase (TRAP) | Includes combined immunodeficiency with autoimmunity and spondylometaphyseal dysplasia [MIM 607944] |
| Condition (Disease) | Type | OMIM Number | Gene | Protein Name | Description |
|--------------------|------|-------------|------|--------------|-------------|
| Odontochondrodysplasia (OCD) | AR | 184260 | | | |
| SMD, Sutcliffe type or corner fractures type | AD | 184255 | | | |
| SMD with cone-rod dystrophy | AR | 608940 | PCYT1A | Phosphate cytidylyltransferase 1 | Some cases are linked to COL2A1 but not the original family |
| SMD with retinal degeneration, axial type | AR | 602271 | | | |
| See also SMD Kozlowski (group TRPV4) as well as SMD Sedaghatian type in group 14; there are many individual reports of SMD variants. |
| 13. Spondylo-epi-(meta)-physeal dysplasias (SE(M)D) | | | | | |
| Dyggve–Melchior–Clausen dysplasia (DMC) | AR | 223800 | DYM | Dymeclin | Includes Smith–McCort dysplasia (MIM 607326) |
| Immuno-osseous dysplasia (Schimke) | AR | 242900 | SMARCAL1 | SWI/SNF-related regulator of chromatin subfamily A-like protein 1 |
| SED, Wolcott–Rallison type | AR | 226980 | EIF2AK3 | Translation initiation factor 2-alpha kinase-3 |
| SEMD, Matrilin type | AR | 608728 | MATN3 | Matrilin 3 |
| SEMD, short limb–abnormal calcification type | AR | 271665 | DDR2 | Discoidin domain receptor family, member 2 |
| SED tarda, X-linked (SED-XL) | XLR | 313400 | SEDL | Sedlin |
| CODAS syndrome | | | | | |
| See also: Opsismodysplasia (group 14), mucopolysaccharidosis type 4 (Morquio syndrome) and other conditions in group 27, as well as PPRD (SED with progressive arthropathy) in group 31 |
| 14. Severe spondylodysplastic dysplasias | | | | | |
| Achondrogenesis type 1A (ACG1A) | AR | 200600 | TRIP11 | Golgi-microtubule-associated protein, 210-KD, GMAP210 | Includes lethal and milder cases |
| Schneckenbecken dysplasia | AR | 269250 | SLC35D1 | Solute carrier family 35 member D1; UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter |
| Spondylometaphyseal dysplasia, Sedaghatian type | AR | 250220 | GPX4 | Glutathione peroxidase 4 |
| Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like) | AR | 258480 | INPP1 | Inositol polyphosphate phosphatase-like 1 |
| Opsismodysplasia | AR | 258480 | MAGMAS | Presequence translocase-associated motor 16 |

(Continued)
| Group/Name of Disorder | Inheritance | MIM No. | Locus or Gene | Protein | Notes |
|------------------------|-------------|---------|---------------|---------|-------|
| 15. Acromelic dysplasias |             |         |               |         |       |
| Acrocapitofemoral dysplasia | AR    | 607778 | IHH | Indian hedgehog |       |
| Geleophysic dysplasia    | AR    | 231050 | ADAMTS1,2 | ADAMTS-like protein 2 | Some forms unlinked to either gene |
| Acromelic dysplasia      | AD    | 161485 | FBN1 | Fibrillin 1 | Includes acral anomalies dysplasia, previously known as Fantasy Island dysplasia or Tattoo dysplasia |
| Weill–Marchesani         | AD    | 1309210 | SMAD4 | Mothers against decapentaplegic, drosophila, homolog of, 4 | Possibly related or allelic to Brachydactyly type C |
| Acrodysostosis           | AD    | 101800 | POE4D | Phosphodiesterase 4D, camp-specific | Includes some cases of acroscyphodysostosis |
| Angel-shaped phalango-epiphyseal dysplasia [ASPED] | AD | 105835 | PRKAR1A | Protein kinase, camp-dependent, regulatory, type 1, alpha | Includes some cases of acroscyphodysostosis |
| Albright hereditary osteodystrophy | AD | 103580 | GNAS | Guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1 | Includes some cases of acroscyphodysostosis |

See also brachydactyly group [group 37]

16. Acromesomelic dysplasias

| Group/Name of Disorder | Inheritance | MIM No. | Locus or Gene | Protein | Notes |
|------------------------|-------------|---------|---------------|---------|-------|
| Acromesomelic dysplasia type Maroteaux (AMDM) | AR    | 602875 | NPR2 | Natriuretic peptide receptor 2 | Includes acromesomelic dysplasia Hunter–Thompson type; see also Brachydactylies [group 34] |
| Grebe dysplasia         | AR    | 2000700 | GDF5 | Growth and Differentiation Factor 5 | See also Brachydactylies [group 34] |
| Fibular hypoplasia and complex brachydactyly (Du Pan) | AR    | 228900 | GDF5 | Growth and Differentiation Factor 5 | See also Brachydactylies [group 34] |
| Acromesomelic dysplasia with genital anomalies | AR    | 609441 | BMPR1B | Bone morphogenetic protein receptor 1B | See also Brachydactylies [group 34] |
| Acromesomelic dysplasia, Osebold-Remondini type | AD    | 112910 |         |         |       |

17. Mesomelic and rhizo-mesomelic dysplasias

| Group/Name of Disorder | Inheritance | MIM No. | Locus or Gene | Protein | Notes |
|------------------------|-------------|---------|---------------|---------|-------|
| Dyschondrosteosis (Leri–Weill) | Pseudo-AD | 127300 | SHOX | Short stature–homeobox gene | Includes Reinhardt–Pfeiffer dysplasia, MIM 191400 |
| Langer type (homozygous dyschondrosteosis) | Pseudo-AR  | 249700 | SHOX | Short stature–homeobox gene |       |
| Disorder                                                                 | Mode of Inheritance | Reference      | Gene/Protein                                                                 | Description                                                                 |
|-------------------------------------------------------------------------|---------------------|----------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Omodysplasia                                                            | AR                  | 258315         | GPC6 Glypican 6                                                               | Receptor tyrosine kinase-like orphan receptor 2                              |
| Omodysplasia, dominant                                                  | AD                  | 164745         | FZD2 Frizzled 2                                                               | Includes previous CDVESDEM (costo–vertebral segmentation defect with mesomelia); see also brachydactyly type B |
| Robinow syndrome, recessive type                                         | AR                  | 268310         | ROR2 Receptor tyrosine kinase-like orphan receptor 2                          |                                                                           |
| Robinow syndrome, dominant type                                          | AD                  | 180700         | WNTSA Wingless-type mmtv integration site family, member 5a                   |                                                                           |
| Mesomelic dysplasia, Kantaputra type                                     | AD                  | 601365         | DVL1 Dishevelled 1                                                            | Includes Mesomelic dysplasia, Korean type                                    |
| Mesomelic dysplasia, Nievergelt type                                     | AD                  | 163400         |                                                                           |                                                                           |
| Mesomelic dysplasia, Kozlowski–Reardon type                             | AR                  | 249710         |                                                                           |                                                                           |
| Mesomelic dysplasia with acral synostoses (Verloes–David–Pfeiffer type) | AD                  | 600383         | SULF1 and SLCOSA1 Heparan sulfate 6-0-endo-sulfatase 1 and solute carrier organic anion transporter family member SA1 | Microdeletion syndrome involving two adjacent genes                         |
| Mesomelic dysplasia, Savarirayan type (Triangular Tibia–Fibular Aplasia) | SP                  | 605274         | 6p22.3 deletions                                                            | Possibly related to Nievergelt dysplasia.                                   |
| Campomelic dysplasia and related disorders                               |                     |                |                                                                             |                                                                           |
| Campomelic dysplasia (CD)                                               | AD                  | 114290         | SOX9 SRY-box 9                                                               | Includes acampomelic campomelic dysplasia (ACD), mild campomelic dysplasia (MIM 602196) and isolated Pierre–Robin |
| Stüve–Wiedemann dysplasia                                               | AR                  | 601559         | LIFR Leukemia Inhibitory Factor Receptor                                     | Includes former neonatal Schwartz–Jampel syndrome or SJS type 2             |
| Kyphomelic dysplasia, several forms                                     |                     | 211350         |                                                                             | Probably heterogeneous                                                       |
| 3-M syndrome                                                            | AR                  | 273750         | CUL7 Culin 7                                                                 | Includes dolichospondyl dysplasia and Yakut short stature syndrome           |
| Kenny–Caffey dysplasia                                                  | AR                  | 244460         | TBCE Tubulin-specific chaperone E                                            | Referred to in OMIM as type 1 but does not correspond to disorder described by Kenny and Caffey which is the dominant form |
| Kenny–Caffey dysplasia                                                  | AD                  | 127000         | FAM111A Family with sequence similarity 111, member A                      |                                                                           |
| Osteocraniostenosis                                                     | AR                  | 602361         | FAM111A Family with sequence similarity 111, member A                      |                                                                           |
| Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)     | AR                  | 210710         | RNU4ATAC RNA, U4ATAc small nuclear                                          | Includes Taybi–Linder cephaloskeletal dysplasia                             |
| Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type) | AR                  | 210720         | PCNT2 Pericentrin 2                                                          |                                                                           |
| IMAGE syndrome (intrauterine growth retardation,                        | AD                  | 614732         | CDKN1C Cyclin-dependent kinase inhibitor                                     | Possibly heterogeneous                                                       |

(Continued)
| Group/Name of Disorder | Inheritance | MIM No. | Locus or Gene | Protein | Notes |
|------------------------|-------------|---------|---------------|---------|-------|
| metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies | | | | |
| 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 centre in digit 2) | AR | 251450 | CANT1 | Calcium-activated nucleotidase 1 |
- Desbuquois dysplasia with short metacarpals and elongated phalanges (Kim type) | AR | 251450 | CANT1 | Calcium-activated nucleotidase 1 |
- Desbuquois dysplasia type 2 | AR | | | |
- Pseudodiastrophic dysplasia | AR | 264180 | | |
- SEMD with joint laxity (SEMD-JL) leptodactylic or Hall type | AD | 603546 | KIF22 | Kinesin family member 22 |
- SEMD with joint laxity (SEMD-JL) Beighton type | AR | 271640 | B3GALT6 | Beta-1,3-galactosyltransferase polypeptide 6 |

See also: SED with congenital dislocations, CHST3 type (group 4); Atelosteogenesis type 3 and Larsen syndrome (group 7)

**21. Chondrodysplasia punctata (CDP) group**

- CDP, X-linked dominant, Conradi-Hünermann type (CDPX2) | XLD | 302960 | EBP | Emopamil-binding protein |
- CDP, X-linked recessive, brachytelephalangic type (CDPX1) | XLR | 302950 | ARSE | Arylsulfatase E |
- CHILD [congenital hemidysplasia, ichthyosis, limb defects] | XLD | 308050 | NSDHL | NAD[P]H steroid dehydrogenase-like protein |
- Keutel syndrome | AR | 245150 | MGP | Matrix gamma-carboxyglutamic acid |
- Greenberg dysplasia | AR | 215140 | LBR | Lamin B receptor, 3-beta-hydroxysterol delta (14)-reductase |

- Rhizomelic CDP type 1 | AR | 215100 | PEX7 | Peroxisomal PTS2 receptor |
- Rhizomelic CDP type 2 | AR | 222765 | DHPAT | Dihydroxyacetonephosphate acyltransferase (DHA PAT) |
- Rhizomelic CDP type 3 | AR | 600121 | AGPS | Alkylglycerone-phosphate synthase (AGPS) |
- CDP tibial-metacarpal type | AD/AR | | | |
- Astley–Kendall dysplasia | AR? | 118651 | | |

Note that stippling can occur in maternal auto-immune disease and several syndromes such as Zellweger, Smith–Lemli–Opitz and others. See also desmosterolosis as well as SEMD short limb-abnormal calcification type in group 13.

**22. Neonatal osteosclerotic dysplasias**

- Blomstrand dysplasia | AR | 215045 | PTH1R | PTH/PTHrP receptor 1 |

Caused by recessive inactivating
| Condition                                      | Mode of Inheritance | Catalog Number | Gene/Protein          | Description                                                                 |
|------------------------------------------------|---------------------|----------------|-----------------------|----------------------------------------------------------------------------|
| Desmosterolosis                                | AR                  | 602398         | DHCR24                | 3-beta-hydroxysterol delta-24-reductase                                    |
| Caffey disease (including prenatal, infantile and attenuated forms) | AD                  | 114000         | COL1A1                | Collagen 1, alpha-1 chain                                                  |
| Caffey dysplasia (severe variants with prenatal onset) | AR                  | 114000         |                       |                                                                             |
| Raine dysplasia (lethal and non-lethal forms)   | AR                  | 259775         | FAM20C                | Dentin matrix protein 4                                                   |
| See also Astley–Kendall dysplasia and CDPs in group 21 |                     |                |                       |                                                                             |
| **23. Osteopetrosis and related disorders**     |                     |                |                       |                                                                             |
| Osteopetrosis, severe neonatal or infantile forms (OPTB1) | AR                  | 259700         | TICRG1                | Subunit of ATPase proton pump                                             |
| Osteopetrosis, severe neonatal or infantile forms (OPTB4) | AR                  | 611490         | CLCN7                 | Chloride channel 7                                                        |
| Osteopetrosis, severe neonatal or infantile forms (OPTB8) | AR                  | 615085         | SNX10                 | Sorting Nexin 10                                                          |
| Osteopetrosis, infantile form, with nervous system involvement (OPTB5) | AR                  | 259720         | OSTM1                 | Grey lethal/Osteopetrosis associated transmembrane protein                |
| Osteopetrosis, intermediate form, osteoclast-poor (OPTB2) | AR                  | 259710         | RANKL (TNFSF11)       | Receptor activator of NF-kappa-B ligand with tumor necrosis factor ligand superfamily, member 11 |
| Osteopetrosis, infantile form, osteoclast-poor with immunoglobulin deficiency (OPTB7) | AR                  | 612302         | RANK (TNFRSF11A)      | Receptor activator of NF-kappa-B                                          |
| Osteopetrosis, intermediate form (OPTB6)        | AR                  | 611497         | PLEKHM1               | Pleckstrin homology-domain-containing protein, family M, member 1         |
| Osteopetrosis, intermediate form (OPTA2)        | AR                  | 259710         | CLCN7                 | Chloride channel pump                                                      |
| Osteopetrosis with renal tubular acidosis (OPTB3) | AR                  | 259730         | CA2                   | Carbonic anhydrase 2                                                       |
| Osteopetrosis, late-onset form type 1 (OPTA1)   | AD                  | 607634         | LRPS                  | Low density lipoprotein receptor-related protein 5                        |
| Osteopetrosis, late-onset form type 2 (OPTA2)   | AD                  | 166600         | CLCN7                 | Chloride channel 7                                                        |
| Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID) | XL                  | 300301         | IKKG (NEMO)           | Inhibitor of kappa light polypeptide gene enhancer, kinase of             |
| Osteopetrosis, moderate form with defective leucocyte adhesion (LAD3) | AR                  | 612840         | FERM13 (KIND3)        | Fermitin 3 (Kindlin 3)                                                    |
| Osteopetrosis, moderate form with defective leucocyte adhesion | AR                  | 612840         | RASGRP2 (Ca2/1DG-GEF1) | Ras guanyl nucleotide-releasing protein 2                                  |
| Pyknodysostosis                                | AR                  | 265800         | CTSK                  | Cathepsin K                                                               |
| Osteopoikilosis                                | AD                  | 155950         | LEMD3                 | LEM domain-containing 3                                                    |
| Melorheostosis with osteopoikilosis            | AD                  | 155950         | LEMD3                 | LEM domain-containing 3                                                    |
| Osteopathia striata with cranial sclerosis (OSCS) | XLD                 | 300373         | WTX                   | FAM123B                                                                  |
| Melorheostosis                                 | SP                  |                |                       |                                                                           |
| Dysostosclerosis                               | AR                  | 224300         | SLC29A3               | Solute carrier family 29 (nucleoside transporter)                          |

(Continued)
| Group/Name of Disorder                                                                 | Inheritance | MIM No.  | Locus or Gene | Protein                                                                 | Notes                                                                 |
|--------------------------------------------------------------------------------------|-------------|----------|---------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| **24. Other sclerosing bone disorders**                                               |             |          |               |                                                                         |                                                                      |
| Craniometaphyseal dysplasia, autosomal dominant type                                  | AD          | 123000   | ANKH          | Homolog of mouse ANK (ankylosis) gene                                   | Gain of function mutations                                          |
| Diaphyseal dysplasia Camurati–Engelmann                                              | AD          | 131300   | TGFBR1        | Transforming growth factor beta 1                                        |                                                                      |
| Hematodiaphyseal dysplasia Ghosal                                                    | AR          | 231095   | TBXAS1        | Thromboxane A synthase 1                                               |                                                                      |
| Hypertrophic osteoarthropathy                                                        | AR          | 259100   | HPGD          | 15-alpha-hydroxyprostaglandin dehydrogenase                             |                                                                      |
| Pachydermoperiostosis [hypertrophic osteoarthropathy, primary, autosomal dominant]  | AD          | 167100   |              |                                                                         |                                                                      |
| Oculo-dento-osseous dysplasia [DDDD] mild type                                        | AD          | 164200   | GJA1          | Gap junction protein alpha-1                                            |                                                                      |
| Oculo-dento-osseous dysplasia [DDDD] severe type                                     | AR          | 257850   | GJA1          | Gap junction protein alpha-1                                            | Possibly homozygous form of mild ODDD                                  |
| Osteoectasia with hyperphosphatasia (juvenile Paget disease)                          | AR          | 239000   | OPG           | Osteoprotegerin                                                         |                                                                      |
| Sclerosteosis                                                                       | AR,AD       | 269500, 614305 | SOST, LRP4 | Sclerostin, Low density lipoprotein receptor-related protein 4 | Specific 52 kb deletion downstream of SOST                          |
| Endosteal hyperostosis, van Buchem type                                              | AR          | 239100   | SOST          | Sclerostin                                                              |                                                                      |
| Trichodentosseous dysplasia                                                          | AD          | 190320   | DLX3          | Distal-less homeobox 3                                                  | Also known as Hardcastle                                             |
| Craniometaphyseal dysplasia, autosomal recessive type                                 | AR          | 218400   | GJA1          | Gap junction protein alpha-1                                            |                                                                      |
| Diaphysial medullary stenosis with malignant fibrous histiocytoma                    | AD          | 112250   |              |                                                                         |                                                                      |
| Craniodiaphyseal dysplasia                                                           | AD          | 122860   | SOST          | Sclerostin                                                              |                                                                      |
| Craniodiaphyseal dysplasia, Worgian bone type                                        | AR          | 615118   |              |                                                                         | Dominant negative                                                    |
| Endosteal sclerosis with cerebellar hypoplasia                                       | AR          | 213002   |              |                                                                         | Also known as Schwartz–Lelek dysplasia                               |
| Lenz-Majewski hyperostotic dysplasia                                                 | SP          | 151050   | PTDSS1        | Phosphatidylyserine synthase 1                                          |                                                                      |
| Metaphyseal dysplasia, Braun–Tinschert type                                         | AD          | 605946   |              |                                                                         |                                                                      |
| Pyle disease                                                                        | AR          | 265900   |              |                                                                         |                                                                      |
| **25. Osteogenesis imperfecta and decreased bone density group**                     |             |          |               |                                                                         |                                                                      |
| *For comments the classification of Osteogenesis imperfecta, please refer to the text*|             |          |               |                                                                         |                                                                      |
| Osteogenesis imperfecta, non-deforming form (OI type 1)                               | AD          |          | COL1A1, COL1A2 | Collagen 1 alpha-1, Collagen 1 alpha-2 chain,                           | Form with persistently blue sclera                                   |
| Osteogenesis imperfecta, perinatal lethal form (OI type 2)                           | AD, AR      |          | COL1A1, COL1A2 | Collagen 1 alpha-2 chain,                                               |                                                                      |
|                                                                                |             |          | CRTAP, LEPRE1 | Cartilage-associated Protein Leucine proline-enriched proteoglycan (leprecan) 1 | See also Bruck syndrome (below)                                    |
|                                                                                |             |          | PPIB          | Peptidylprolyl isomerase B (cyclophilin B)                               |                                                                      |
| Disorder                                                                 | Mode | Ref   | Gene(s)                                      | Associated Proteins                                                                 |
|------------------------------------------------------------------------|------|-------|----------------------------------------------|-------------------------------------------------------------------------------------|
| Osteogenesis imperfecta, progressively deforming type (OI type 3)       | AD, AR |       | COL1A1, COL1A2, CRTAP, LEPRE1, PPBP, SERPINF1 | Serpin peptidase inhibitor, clade H, member 1, BMP1, FKBABP10, PL0D2, SERPINF1, SP7, WNT1, TMEM38B, CREB3L1, SEC24D |
| Osteogenesis imperfecta, moderate form (OI type 4)                      | AD, AR |       | COL1A1, COL1A2, CRTAP, PPBP, FKBABP10, SERPINF1, WNT1, SP7 | Sclerae generally normal                                                             |
| Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus (OI type 5) | AD | 610967 | IFITM5 | Interferon-Induced Transmembrane Protein 5 |
| X-linked osteoporosis                                                  | XL   | 300910 | PL0S3 | Plastin 3 |
| Bruck syndrome type 1 (BS1)                                             | AR   | 259450 | FKBABP10 | FK506 binding protein 10 |
| Bruck syndrome type 2 (BS2)                                             | AR   | 609220 | PL0D2 | Procollagen lysyl hydroxylase 2 |
| Osteoporosis-pseudoglioma syndrome                                      | AR   | 259770 | LRP5 | LDL-receptor related protein 5 |
| LRP5 primary osteoporosis                                              | AD   | 126550 | LRP5 | LDL-receptor related protein 5 |
| Calvarial doughnut lesions with bone fragility                         | AD   | 126550 | LRP5 | LDL-receptor related protein 5 |
| Idiopathic juvenile osteoporosis                                       | SP   | 259750 | LRP5 | LDL-receptor related protein 5 |
| Cole-Carpenter dysplasia (bone fragility with craniosynostosis)        | AD   | 112240 | P4HB | Prolyl 4-hydroxylase, beta-subunit |
| Spondylo-ocular dysplasia                                              | AR   | 605822 | XYL2 | Xylosyltransferase 2 |

(Continued)
| Group/Name of Disorder                                                                 | Inheritance | MIM No. | Locus or Gene | Protein                                                                 | Notes                                                                 |
|--------------------------------------------------------------------------------------|-------------|---------|---------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| Osteopenia with radiolucent lesions of the mandible                                  | AD          | 166260  | B4GALT7       | Xylosylprotein 4-beta-galactosyltransferase deficiency                   |                                                                      |
| Ehlers-Danlos syndrome, progeroid form                                               | AR          | 130070  |               |                                                          |                                                                      |
| Geroderma osteodysplasticum                                                           | AR          | 231070  | GORAB         | SCYL1-binding protein 1                                                 |                                                                      |
| Cutis laxa, autosomal recessive form, type 2B (ARCL2B)                                | AR          | 612940  | PYCR1         | Pyrroline-5-carboxylate reductase 1                                     |                                                                      |
| Cutis laxa, autosomal recessive form, type 2A (ARCL2A) [Wrinkly skin syndrome]       | AR          | 278250, 219200 | ATP6V0A2     | ATPase, H+ transporting, lysosomal, V0 subunit A2                        |                                                                      |
| Singleton–Merten dysplasia                                                           | AD          | 182250  |               |                                                          |                                                                      |
| Hypophosphatasia, perinatal lethal, infantile and juvenile forms                     | AR          | 241500  | ALPL          | Alkaline phosphatase, tissue non-specific (TNSALP)                      | Intrafamilial variability                                             |
| Hypophosphatasia, juvenile and adult forms                                            | AD          | 146300  | ALPL          | Alkaline phosphatase, tissue non-specific (TNSALP)                      | Includes odontohypophosphatasia                                       |
| Hypophosphatemic rickets, X-linked dominant                                          | XLD         | 307800  | PHEX          | X-linked hypophosphatemia membrane protease                             |                                                                      |
| Hypophosphatemic rickets, autosomal dominant                                         | AD          | 193100  | FGF23         | Fibroblast growth factor 23                                             |                                                                      |
| Hypophosphatemic rickets, autosomal recessive, type 1 [ARHR1]                       | AR          | 241520  | DMP1          | Dentin matrix acidic phosphoprotein 1                                  |                                                                      |
| Hypophosphatemic rickets, autosomal recessive, type 2 [ARHR2]                       | AR          | 613312  | ENPP1         | Ectonucleotide pyrophosphatase/phosphodiesterase 1                      |                                                                      |
| Hypophosphatemic rickets with hypercalcuiuria, X-linked recessive                    | XLR         | 300554  | CICN5         | Chloride channel 5                                                      | Part of Dent’s disease complex                                        |
| Hypophosphatemic rickets with hypercalcuiuria, autosomal recessive [HHRH]            | AR          | 241530  | SLC34A3       | Sodium-phosphate cotransporter                                         |                                                                      |
| Neonatal hyperparathyroidism, severe form                                             | AR          | 239200  | CASR          | Calcium-sensing receptor                                                |                                                                      |
| Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism     | AD          | 145980  | CASR          | Calcium-sensing receptor                                                |                                                                      |
| Calcium pyrophosphate deposition disease [familial chondrocalcinosis] type 2          | AD          | 118600  | 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 [Hurler, Hurler–Scheie, Scheie]                   | AR          | 607014  | IDA           | Alpha-1-Iduronidase                                                     |                                                                      |
| Mucopolysaccharidosis type 2 [Hunter]                                              | XLR         | 309900  | IDS           | Iduronate-2-sulfatase                                                  |                                                                      |
| Mucopolysaccharidosis type 3A [Sanfilippo A]                                      | AR          | 252900  | HSS           | Heparan sulfate sulfatase                                              |                                                                      |
| Mucopolysaccharidosis type 3B [Sanfilippo B]                                      | AR          | 252920  | NAGLU         | N-Ac-beta-D-glucosaminidase                                             |                                                                      |
| Mucopolysaccharidosis type 3C [Sanfilippo C]                                      | AR          | 252930  | HSGNAT        | Ac-CoA: alpha-glucosaminide N-acetyltransferase                        |                                                                      |
| Condition                                         | Code   | Enzyme/Protein Description |
|--------------------------------------------------|--------|-----------------------------|
| Mucopolysaccharidosis type 3D (Sanfilippo D)     | AR 252940 | GNS  N-Acetylglucosamine 6-sulfatase |
| Mucopolysaccharidosis type 4A (Morquio A)        | AR 253000 | GALNS Galactosamine-6-sulfate sulfatase |
| Mucopolysaccharidosis type 4B (Morquio B)        | AR 253010 | GLBI Beta-Galactosidase |
| Mucopolysaccharidosis type 6 (Maroteaux-Lamy)    | AR 253220 | ARSB Arylsulfatase B |
| Mucopolysaccharidosis type 7 (Sly)               | AR 230000 | FUCB Alpha-Fucosidase |
| Alcohol-Mannosidosis                              | AR 248500 | MANA Alcohol-Mannosidase |
| Beta-Mannosidosis                                 | AR 248510 | MANB Beta-Mannosidase |
| Aspartylglucosaminuria                           | AR 208400 | AGA Aspartyl-glucosaminidase |
| GMI Gangliosidosis, several forms                | AR 230500 | GLB1 Beta-Galactosidase |
| Sialidosis, several forms                        | AR 256550 | NEU1 Neuraminidase (sialidase) |
| Sialic acid storage disease (SASD)               | AR 269920 | SLC17A5 Sialin [sialic acid transporter] |
| Galactosialidosis, several forms                 | AR 256540 | PPGB Beta-Galactosidase protective protein |
| Multiple sulfatase deficiency                    | AR 272200 | SUMF1 Sulfatase-modifying factor-1 |
| Mucolipidosis II (I-cell disease), alpha/beta type| AR 252500 | GNPTAB N-Acetylglucosamine 1-phosphotransferase, alpha/beta subunits |
| Mucolipidosis III (Pseudo–Hurler polydystrophy), alpha/beta type| AR 252600 | GNPTAB N-Acetylglucosamine 1-phosphotransferase, alpha/beta subunits |
| Mucolipidosis III (Pseudo–Hurler polydystrophy), gamma type| AR 252605 | GNPTG N-Acetylglucosamine 1-phosphotransferase, gamma subunit |

### 28. Osteolysis group

| Condition                                         | Code   | Gene/Mutation |
|--------------------------------------------------|--------|---------------|
| Familial expansile osteolysis                     | AD 174810 | RANK [TNFRSF11A] |
| Mandibuloacral dysplasia type A                   | AD 248370 | LMNA Lamin A/C |
| Mandibuloacral dysplasia type B                   | AR 608612 | ZMPSTE24 Zinc metalloproteinase |
| Progeria, Hutchinson–Giford type                  | AD 176670 | LMNA Lamin A/C |
| Torg–Winchester syndrome                          | AR 259600 | MMP2 Matrix metalloproteinase 2 |
| Hajdu–Cheney syndrome                             | AD 102500 | NOTCH2 NOTCH2 |
| Multicentric carpal-tarsal osteolysis with and without nephropathy | AD 166300 | MAFB V-maf musculoaponeurotic fibrosarcoma oncogene family, protein b |

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

### 29. Disorganized development of skeletal components group

| Condition                                         | Code   | Gene/Mutation |
|--------------------------------------------------|--------|---------------|
| Multiple cartilaginous exostoses 1                | AD 133700 | EX1 EXT1 Exostosin-1 |
| Multiple cartilaginous exostoses 2                | AD 133701 | EXT2 Exostosin-2 |
| Multiple cartilaginous exostoses 3                | AD 600209 | EX7 EX2 Exostosin-2 |

Unclear if other genes/loci

(Continued)
| Group/Name of Disorder                                      | Inheritance | MIM No. | Locus or Gene | Protein                                      | Notes                                           |
|------------------------------------------------------------|-------------|---------|---------------|----------------------------------------------|------------------------------------------------|
| Cherubism                                                 | AD          | 118400  | SH3BP2        | SH3 domain-binding protein 2                 | Somatic mosaicism and imprinting phenomena     |
| Fibrous dysplasia, polyostotic form (McCune–Albright)     | SP          | 174800  | GNAS          | Guanine nucleotide-binding protein, alpha-stimulating activity subunit 1 |                                             |
| Progressive osseous heteroplasia                          | AD          | 166350  | GNAS          | Guanine nucleotide-binding protein, alpha-stimulating activity subunit 1 | Gene subject to imprinting                     |
| Gnathodiaphyseal dysplasia                                | AD          | 166260  | TMEM16E       | Transmembrane protein 16E                     |                                               |
| Metachondromatosis                                        | AD          | 156250  | PTPN11        | Protein-tyrosine phosphatase non-receptor-type 11 |                                             |
| Osteoglophonic dysplasia                                 | AD          | 166250  | FGFR1         | Fibroblast growth factor receptor 1          | See also Craniosynostosis syndromes in group 30 |
| Fibrodysplasia ossificans progressiva (FOP)               | AD, SP      | 135100  | ACVR1         | Activin A (BMP type 1) receptor              |                                               |
| Neurofibromatosis type 1 (NF1)                            | AD          | 162200  | NF1           | Neurofibromin                                |                                               |
| Carpotarsal osteochondromatosis                           | AD          | 127820  |              |                                              |                                               |
| Cherubism with gingival fibromatosis (Ramon syndrome)     | AR          | 266270  |              |                                              |                                               |
| Dysplasia epiphysealis hemimelica (Trevor)                | SP          | 127800  |              |                                              |                                               |
| Lipomembranous osteodystrophy with leukoencephalopathy [presenile dementia with bone cysts; Nasu–Hakola] | AR          | 221770  | TREM2, TYROBP | Triggering receptor expressed on myeloid cells 2, Tyro protein tyrosine kinase-binding protein | Role of PTHR1 mutations found in a few cases only, role still unclear |
| Enchondromatosis [Ollier] and Enchondromatosis with hemangiomata [Maffucci] | SP          | 166000  | IDH1, IDH2    | Isocitrate dehydrogenase 1, 2                 |                                               |
| Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria | SP          | 614875  | IDH1, IDH2    | Isocitrate dehydrogenase 1, 2                 |                                               |
| Genochondromatosis                                         | SP/AD       | 137360  |              |                                              |                                               |
| Gorham-Stout                                              |             |         |               |                                              |                                               |
| See also: Proteus syndrome in group 30;                   |             |         |               |                                              |                                               |
| Spondyloenchondrodysplasia in group 12;                   |             |         |               |                                              |                                               |
| 30. Overgrowth (tall stature) syndromes with skeletal involvement |             |         |               |                                              |                                               |
| Weaver syndrome                                           | SP/AD       | 277590  | EZH2          | Enhancer of zeste, drosophila, homolog 2      | Some cases reported with NSD1 mutations [see Sotos syndrome] |
| Sotos syndrome                                            | AD          | 117550  | NSD1          | Nuclear receptor-binding su-var, enhancer of zeste, and trithorax domain protein 1 | Some cases may have NFIX mutations [see Marshall–Smith syndrome] |
| Sotos-like syndrome                                       | AD          | 602535  | SETD2         | Set domain containing protein2 nuclear factor I/X | Some clinical overlap with Sotos syndrome [see above] |
| Marshall–Smith syndrome                                   | SP          | 176920  | AKT1          | v-akt murine thymoma viral oncogene homolog 1 | Some Proteus-like cases have mutations in the PTEN gene |
| Proteus syndrome                                           | SP          | 612918  | PIK3CA        | Phosphatidylinositol 3-kinase, catalytic, alpha |                                               |
| CLOVES                                                    | SP          | 154700  | FBN1          | Fibrillin 1                                  |                                               |
| Marfan syndrome                                           | AD          | 121050  | FBN2          | Fibrillin 2                                  |                                               |
| Disorder                                                                 | Genetics | Gene | Protein                                      | Description                                                                 |
|-------------------------------------------------------------------------|----------|------|----------------------------------------------|-----------------------------------------------------------------------------|
| Loeys–Dietz syndrome types 1A, 1B, 2A, 2B, 3, 4                          | AD       | TGFBR1, TGFBR2, SMAD3, TGFBR2 | TGFbeta subunit 1, TGFbeta subunit 2, SMA related protein 3, TGFbeta 2   |
| Overgrowth syndrome with 2q37 translocations                            | SP       | NPPC | Natriuretic peptide precursor C             | Overgrowth probably caused by overexpression of NPPC                       |
| Overgrowth with macrodactyly and NPR2 gain of function                  | AD       | NPR2 | Natriuretic peptide receptor 2             | Nosologic status unclear but conspicuous skeletal phenotype(s)             |
| Overgrowth syndrome with skeletal dysplasia (Nishimura–Schmidt, endochondral gigantism) | SP       | NPPC | Natriuretic peptide precursor C             |                                                                             |
| See also: Shprintzen–Goldberg syndrome in Craniosynostosis group         |          |      |                                              |                                                                             |
| 31. Genetic inflammatory/rheumatoid-like osteoarthropathies              |          |      |                                              |                                                                             |
| Progressive pseudorheumatoid dysplasia (PPRD; SED with progressive arthropathy) | AR       | WISP3 | WNT1-inducible signaling pathway protein 3 |                                                                             |
| Chronic infantile neurologic cutaneous articular syndrome (CINCA)/neonatal onset multisystem inflammatory disease (NOMID) | AD       | CIAS1 | Cryopyrin                                   |                                                                             |
| Sterile multifocal osteomyelitis, periostitis, and pustulosis (CINCA/NOMID-like) | AR       | IL1RN | Interleukin 1 receptor antagonist           |                                                                             |
| Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anemia (CRMO with CDA; Majeed syndrome) | AR       | LPIN2 | Lipin 2                                     |                                                                             |
| Hyperostosis/hyperphosphatemia syndrome                                  | AR       | GALNT3 | UDP-N-acetyl-alpha-D-XYLOPYRANOSAMINE:POLYPEPTIDE N-ACETYLGLUCOSAMINYLTRANSFERASE 3 | |
| Hylaine fibromatosis syndrome                                             | AR       | ANTXR2 | Anthrax toxin receptor 2                   | Previously known as Infantile systemic hyalinosis, Juvenile Hylaine Fibromatosis (JHF, 228600) and Puretic syndrome |
| 32. Cleidocranial dysplasia and related disorders                         |          |      |                                              |                                                                             |
| Cleidocranial dysplasia                                                  | AD       | RUNX2 | Runt related transcription factor 2         |                                                                             |
| CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, genital anomalies, skin eruption) | AR       | RUNX2 | Runt related transcription factor 2         |                                                                             |
| Yunis–Varon dysplasia                                                    | AR       | FIG4  | Aristaless-like 4                          | See also Frontonasal dysplasia type 1 (group 34)                           |
| Parietal foramina (isolated)                                             | AD       | ALX4  | Muscle segment homeobox 2                  |                                                                             |
| See also: pycnodysostosis, wrinkly skin syndrome, and several others. See also metaphyseal dysplasia with maxillary hypoplasia in Group 11 |          |      |                                              |                                                                             |
| 33. Craniosynostosis syndromes                                           |          |      |                                              |                                                                             |
| Pfeiffer syndrome (FGFR1-related)                                        | AD       | FGFR1 | Fibroblast growth factor                   | Most have FGFR1 P252R mutation                                             |

(Continued)
### Table I.

| Group/Name of Disorder | Inheritance | MIM No. | Locus or Gene | Protein Notes | Notes |
|------------------------|-------------|---------|---------------|---------------|-------|
| Apert syndrome         | AD          | 101200  | FGFR2         | Fibroblast growth factor receptor 1 and 2 | Includes Jackson–Weiss syndrome (MIM 123150) and Antley–Bixler variants caused by FGFR2 mutations [see below] |
| Craniosynostosis with cutis gyrata (Beare–Stevenson) | AD | 123790 | FGFR2 | Fibroblast growth factor receptor 2 | Defined by specific FGFR3 A391E mutation |
| Crouzon syndrome       | AD          | 123500  | FGFR2         | Fibroblast growth factor receptor 2 | Defined by specific FGFR3 P250R mutation |
| Bent bone dysplasia    | AD          | 614592  | FGFR2         | Fibroblast growth factor receptor 2 | Similar cases with FGFR2 mutations classified by MIM as Antley–Bixler without genital anomalies may be variants of Pfeiffer syndrome |
| Crouzon-like craniosynostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome) | AD | 612247 | FGFR3 | Fibroblast growth factor receptor 3 | Heterozygous P148H mutation in a two families |
| Craniosynostosis, Muenke type | AD | 602849 | FGFR3 | Fibroblast growth factor receptor 3 | RECOL4 might not account for all cases of Baller–Gerold |
| Antley–Bixler syndrome | AR          | 201750  | POR           | Cytochrome P450 oxidoreductase | |
| Craniosynostosis Boston type | AD | 604757 | MSX2 | MSX2 | |
| Saethre–Chotzen syndrome | AD  | 101400 | TWIST1 | TWIST | |
| Shprintzen–Goldberg syndrome | AD | 182212 | SKI | SKI | |
| Baller–Gerold syndrome | AR          | 218600  | RECOL4        | RECO Protein-like 4 | |
| Carpenter syndrome     | AR          | 201000  | RAB23         | | |
| Coronal craniosynostosis | AD  | 615314 | TCF12 | Transcription factor 12 | |
| Complex craniosynostosis | AD   | 600775 | ERF | ETS2 repressor factor | |

### 34. Dysostoses with predominant craniofacial involvement

| Group/Name of Disorder                                                                 | Inheritance | MIM No. | Locus or Gene | Protein Notes                                                                 | Notes |
|----------------------------------------------------------------------------------------|-------------|---------|---------------|--------------------------------------------------------------------------------|-------|
| Mandibulo-facial dysostosis (Treacher Collins, Franceschetti–Klein)                    | AD, AD, AR  | 154500 | TCOF1, POLR1D, POLR1C | Treacher Collins–Franceschetti syndrome 1, Polymerase (RNA) I polypeptide D, Polymerase (RNA) I polypeptide C | |
| Oral-facial-digital syndrome type 1 (OFD1)                                              | XLR         | 311200 | CKORF5       | chr. X open reading frame 5 | |
| Weyers acrofacial (acroental) dysostosis                                                | AD          | 193530 | EVC1, EVC2   | Ellis-van Creveld 1 protein | See also ciliopathy group |
| Endocrine-cerebro-osteodysplasia (ECO)                                                  | AR          | 612651 | ICK          | Intestinal cell kinase | |
| Craniofrontonasal syndrome                                                             | XLD         | 304110 | EFNB1        | Ephetin B1 | |
| Frontonasal dysplasia, type 1                                                          | AR          | 136760 | ALX3         | Aristaless-like-3 |
| Condition                                                      | Inheritance | Gene/Protein                              | Other Remarks                                                                 |
|---------------------------------------------------------------|-------------|-------------------------------------------|------------------------------------------------------------------------------|
| Frontonasal dysplasia, type 2                                 | AR          | ALX4                                      | Includes Goldenhar syndrome and Oculo–Auriculo–Vertebral spectrum; probably genetically heterogeneous |
| Frontonasal dysplasia, type 3                                 | AR          | ALX1                                      |                                                                               |
| Hemifacial microsomia                                         | SP/AD       |                                           |                                                                               |
| Miller syndrome (postaxial acrofacial dysostosis)             | AR          | DHODH                                     |                                                                               |
| Acrofacial dysostosis, Nager type                             | AD/AR       | SF3B4                                     |                                                                               |
| Acrofacial dysostosis, Rodriguez type                         | AR          |                                           |                                                                               |
| Mandibulofacial dysostosis with microcephaly                   | AD          | EFFUD2                                    |                                                                               |
| Hemifacial microsomia                                         | SP/AD       |                                           |                                                                               |
| Miller syndrome (postaxial acrofacial dysostosis)             | AR          | DHODH                                     |                                                                               |
| Acrofacial dysostosis, Nager type                             | AD/AR       | SF3B4                                     |                                                                               |
| Acrofacial dysostosis, Rodriguez type                         | AR          |                                           |                                                                               |
| Mandibulofacial dysostosis with microcephaly                   | AD          | EFFUD2                                    |                                                                               |
| See also Oral-facial-digital syndrome type IV in the Ciliopathies with major skeletal involvement group |            |                                           |                                                                               |
| 35. Dysostoses with predominant vertebral with and without costal involvement |            |                                           |                                                                               |
| Currarino triad                                               | AD          | HX89                                      | Homeobox gene HB9                                                            |
| Spondylocostal dysostosis type 1 (SCD01), type 2 (SCD02), type 3 (SCD03), type 4 (SCD04) | AR          | DLL3                                      | Delta-like 3                                                                  |
| Spondylocostal dysostosis type 5 (SCD05)                       | AD          | MESP2                                     | Mesoderm posterior 2                                                          |
| Spondylothoracic Dysostosis (STD)                             | AR          | MESP2                                     | Mesoderm posterior 2                                                          |
| Vertebral segmentation defect (congenital scoliosis) with variable penetrance | AD          | MESP2                                     | Mesoderm posterior 2                                                          |
| Klippel–Feil anomaly with laryngeal malformation              | AD          | GDF6                                      | Growth and differentiation factor 6 and 3                                     |
| Cerebro-costo-mandibular syndrome (rib gap syndrome)          | AD          | GDF3                                      | Role of GDF6 mutations in dominant spondylothoracic dysostosis unclear         |
| Cerebro-costo-mandibular-like syndrome with vertebral defects  | AR          | MEOX1                                     | Mesenchyme homeobox 1                                                         |
| Diaphanospondylo dysostosis                                  | AR          | BMPER                                     | Small Nuclear Ribonucleoprotein polypeptide B and B-prime                       |
| Spondylomegadiphiaseal-metaphyseal dysplasia (SMMD)            | AR          | NKX3-2                                    | Component of oligomeric Golgi complex 1                                       |
| See also Spondylocarpatal dysplasia in group ?                 |             |                                           | Also classified as CDG type 1                                               |
| 36. Patellar dysostoses                                       |             |                                           | Possibly overlaps with ischiospinal dysostosis                                |
| Ischiopatellar dysplasia (small patella syndrome)             | AD          | TBX4                                      | T-box gene 4                                                                  |
| Nail-patella syndrome                                         | AD          | LMX1B                                     | LIM homeobox transcription factor 1                                           |
| Genitopatellar syndrome                                       | AR?         | KAT6B                                     | Origin recognition complex                                                    |
| Ear-patella-short stature syndrome (Meier–Gorlin)             | AR          | ORC1                                      | Origin recognition complex                                                    |
| See also MED group for conditions with patellar changes as well as ischio-pubic-patellar dysplasia as mild expression |             |                                           |                                                                               |

"(Continued)"
| Group/Name of Disorder of campomelic dysplasia | Inheritance | MIM No. | Locus or Gene | Protein | Notes |
|---------------------------------------------|-------------|---------|---------------|---------|-------|
| 37. Brachydactyly [without extraskeletal manifestations] |             |         |               |         |       |
| Brachydactyly type A1                       | AD          | 112500  | IHH           | Indian Hedgehog |
| Brachydactyly type A1                       | AD          | 112600  | BMPR1B        | Bone Morphogenetic Protein Receptor, 1B |
| Brachydactyly type A2                       | AD          | 112600  | BMP2          | Bone Morphogenetic Protein Type 2 |
| Brachydactyly type A2                       | AD          | 112600  | GDF5          | Growth and Differentiation Factor 5 |
| Brachydactyly type B                        | AD          | 113000  | ROR2          | Receptor Tyrosine Kinase-like Orphan Receptor 2 |
| Brachydactyly type B2                       | AD, AR      | 611377  | NOG           | Noggin |
| Brachydactyly type C                        | AD          | 113100  | GDF5          | Growth and Differentiation Factor 5 |
| Brachydactyly type D                        | AD          | 113200  | HOXD13        | Homeobox D13 |
| Brachydactyly type E                        | AD          | 113300  | PTHLH         | Parathyroid hormone-like hormone (Parathyroid hormone related peptide, PTHRP) |
| Brachydactyly type E                        | AD          | 113300  | HOXD13        | Homeobox D13 |
| Brachydactyly with anonychia [Cooks syndrome] | AD          | 106995  | SOX9          | Regulatory mutations |
| 38. Brachydactylies [with extraskeletal manifestations] |             |         |               |         |       |
| Brachydactylies-mental retardation syndrome  | AD          | 600430  | HDAC4         | Histone deacetylase 4 |
| Hyperphosphatasia with mental retardation, brachytelephalangy, and distinct face | AR | PIGV | Phosphatidylinositol-glycan biosynthesis class V protein (GPI mannosyltransferase 2) |
| Brachydactylies-hypertension syndrome [Bilginturan] | AD | 112410  | PDE3A         | Phosphodiesterase 3A |
| Microcephaly-oculo-digito-esophageal-duodenal syndrome [Feingold syndrome] | AD | 164280  | MYCN | nMYC oncogene |
| Hand-foot-genital syndrome | AD | 140000 | HOXA13 | Homeobox A13 |
| Rubinstein–Taïbi syndrome | AD | 180849 | CREBBP | CREB-Binding Protein |
| Rubinstein–Taïbi syndrome | AD | 180849 | EP300 | E1A-Binding Protein, 300-KD |
| Brachydactyly, Temtamy type | AR | 605282 | CHSY1 | Chondroitin sulfate synthase 1 |
| Christian type brachydactyly | AD | 112450 |             |         |       |
| Coffin–Siris syndrome 1 | AR | 135900 |             |         |       |
| Adams–Oliver | AD | 100300 | ARHGAP31 | | |
| AR | 614219 | DOKK6 | | |
| AD | 614814 | RBPJ | | |
### 39. Limb hypoplasia-reduction defects group

#### Ulnar-mammary syndrome
- De Lange syndrome

| Condition                                      | Type | Gene | Description                                                                 |
|-----------------------------------------------|------|------|------------------------------------------------------------------------------|
| Catel–Manzke syndrome                         | AR   | 615297 | **AR 615297** **EOGT** TDP-Glucose 4,6 Dehydratase See also Chondrodysplasia gPAPP type in Group 4 |
| See also group 20 for other conditions with brachydactyly as well as brachytelephalangic CDP. |

#### Fanconi anemia
- **[see note below]**

| Condition                                      | Type | Gene | Description                                                                 |
|-----------------------------------------------|------|------|------------------------------------------------------------------------------|
| Thrombocytopenia-absent radius (TAR)          | AR   | 274000 | **RBM8A** Thrombopoietin                                                   |
| Thrombocytopenia with distal limb defects     | AD   | 181450 | **TBX3** T-box gene 3                                                       |
| Holt-Oram syndrome                            | AD   | 142900 | **TBX5** T-box gene 5                                                       |
| Okihiro syndrome (Duane–radial ray anomaly)   | AD   | 607323 | **SALL4** SAL-like 4                                                         |
| Cousin syndrome                               | AR   | 260660 | **TBX15** T-box gene 15                                                     |
| Roberts syndrome                              | AR   | 268300 | **ESCO2** Homolog of Establishment of Cohesion - 2                          |
| Split-hand-foot malformation with long bone deficiency (SHFLD3) | AD | 612576 | **BHLHA9** Duplications                                                    |
| Tibial hemimelia                              | ?    | 275220 | **SHH-ZRS** Putative receptor protein                                        |
| Tibial hemimelia-polysyndactyly-triphalangeal thumb | AD | 188740 | **LMBR1** Partial LMBR1 deletion affecting expression of Sonic Hedgehog (SHH) gene |
| Acheiropodia                                   | AR   | 200500 | **WNT3** Wingless-type MMTV integration site family, member 3               |
| Tetra-amelia                                   | AR   | 273395 | **WNT7A** Wingless-type MMTV integration site family, member 7A               |
| Terminal transverse defect                     | ?    | 102650 | **WNT3** Wingless-type MMTV integration site family, member 3               |
| Al-Awadi-Raas-Rothschild limb-pelvis hypoplasia-aplasia | AR | 276820 | **WNT7A** Wingless-type MMTV integration site family, member 7A               |
| Fuhrmann syndrome                              | AR   | 228930 | **WNT7A** Wingless-type MMTV integration site family, member 7A               |
| RAPADILINO syndrome                            | AR   | 266280 | **RECOL4** RECO Protein-like 4                                               |
| Poland                                         |      |       |                                                                              |
| Femoral hypoplasia-unusual face syndrome (FHUFS) | SP/AD? | 134780 | Some phenotypic overlap with FFU syndrome (below)                            |
| Femur-fibula-ulna syndrome (FFU)               | SP   | 228200 | Triplications                                                               |
| Hanhart syndrome (Hypoglossia-hypodactyly)    | AD   | 103300 | **BHLHA9**                                                                   |
| Gollop-Wolfgang                                | AD   | 228250 | **BHLHA9**                                                                   |
| Scapulo-iliac dysplasia (Kosenow)              | AD   | 169550 |                                                                              |

**Note:** The particularly complex genetic basis of Fanconi anemia and its complementation groups is acknowledged but not further listed in this Nosology.
| Group/Name of Disorder                                                                 | Inheritance | MIM No. | Locus or Gene             | Protein            | Notes                                      |
|--------------------------------------------------------------------------------------|-------------|---------|---------------------------|--------------------|--------------------------------------------|
| Ectrodactyly with and without other manifestations                                   |             |         |                           |                    |                                            |
| Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC)                           | AD          | 106260  | P63 {TP63}                | Tumor Protein p63 |                                            |
| Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 3 (EEC3)                 | AD          | 604292  | P63 {TP63}                | Tumor Protein p63 |                                            |
| Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 1 (EEC1)                | AD          | 129900  |                           |                    |                                            |
| Ectrodactyly-ectodermal dysplasia-macular dystrophy syndrome (EEM)                    | AR          | 225280  | CDH3                      | Cadherin 3         |                                            |
| Limb-mammary syndrome (including ADULT syndrome)                                      | AD          | 603273  | P63 {TP63}                | Tumor Protein p63 |                                            |
| Split hand-foot malformation, isolated form, type 4 (SHFM4)                          | AD          | 605289  | P63 {TP63}                | Tumor Protein p63 |                                            |
| Split hand-foot malformation, isolated form, type 1 (SHFM1)                          | AD          | 183600  | DLX5 DLX6                 | Distal-less Homebox 5 Distal-less Homebox 6 |                                            |
| Split hand-foot malformation, isolated form, type 3 (SHFM3)                          | AD          | 246560  | 10q                        |                    | Duplications                               |
| Split hand-foot malformation, isolated form, type 5 (SHFMS)                          | AR          | 606708  | WNT10B                    | Wingless-type MMTV integration site family, member ?A |                                            |
| Hartsfield syndrome                                                                  | AD          | 615465  | FGFR1                      | Fibroblast growth factor receptor 1 |                                            |
| Polydactyly-Syndactyly-Triphalangism group                                            |             |         |                           |                    |                                            |
| Preaxial polydactyly type 1 (PPD1)                                                   | AD          | 174400  | SHH-ZRS                   | Sonic Hedgehog    | Regulatory mutation                         |
| Postaxial polydactyly type A                                                         | AD          | 174200  | GLI3                      | Gli-Kruppel Family Member 3 | Most cases are not GLI3 related            |
| Postaxial polydactyly type B                                                        | Complex     |         |                           |                    |                                            |
| Triphalangeal thumb (TPT)-polydactyly syndrome                                       | AD          | 174500  | SHH-ZRS                   | Sonic Hedgehog    | Regulatory mutation                         |
| Preaxial polydactyly type 3 (PPD3)                                                   | AD          | 174600  |                           |                    |                                            |
| Preaxial polydactyly type 4 (PPD4)                                                   | AD          | 174700  | GLI3                      | Gli-Kruppel Family Member 3 |                                            |
| Greig cephalopolysyndactyly syndrome                                                 | AD          | 175700  | GLI3                      | Gli-Kruppel Family Member 3 |                                            |
| Pallister–Hall syndrome                                                             | AD          | 146510  | GLI3                      | Gli-Kruppel Family Member 3 |                                            |
| Synpolydactyly [complex, fibulin1-associated]                                        | AD          | 608180  | FBLN1                     | Fibulin 1          |                                            |
| Synpolydactyly                                                                       | AD          | 186000  | HDX13                     | Homebox D13       |                                            |
| Townes–Brocks syndrome [renal-ear-anal-radial syndrome]                              | AD          | 107480  | SALL1                     | SAL-like 1         |                                            |
| Lacrimo-auriculo-dento-digital syndrome [LADD]                                       | AD          | 149730  | FGFR2                     | Fibroblast growth factor receptor 2 |                                            |
| Lacrimo-auriculo-dento-digital syndrome [LADD]                                       | AD          | 149730  | FGFR3                     | Fibroblast growth factor receptor 3 |                                            |
| Lacrimo-auriculo-dento-digital syndrome [LADD]                                       | AD          | 149730  | FGFR10                    | Fibroblast growth factor 10 |                                            |
| Acrocallosal syndrome                                                               | AR          | 200990  | KIF7                      | Kinesin family member 7 |                                            |
| Acro-pectoral syndrome                                                              | AD          | 605967  |                           |                    |                                            |
| Acro-pectoral-vertebral dysplasia [F-syndrome]                                       | AD          | 102510  | WNT6                      | Wingless-type mmtv integration | Regulatory mutations                          |
| Condition | Inheritance | Gene/Mutation | Notes |
|-----------|-------------|---------------|-------|
| Mirror-image polydactyly of hands and feet (Laurin–Sandrow syndrome) | AD | SHH-ZRS | Sonic Hedgehog Regulatory mutations; some cases unlinked |
| Cenani–Lenz syndactyly | AR | LRP4 | Low density lipoprotein receptor-related protein 4 |
| Cenani–Lenz like syndactyly | SP (AD?) | GREM1, FMN1 | Gremlin 1, Formin 1 |
| Syndactyly, Malik–Percin type | AD | BHLHA9 | |
| STAR syndrome (syndactyly of toes, telecanthus, ano- and renal malformations) | XL | FAM58A | |
| Syndactyly type Lueken | AD | IHH | Indian Hedgehog Regulatory mutations |
| Oculodentodigital dysplasia, Syndactyly type 3 (IV-V) | AD | GJA1 | Gap junction protein alpha-1 |
| Syndactyly Haas type | AD | SHH-ZRS | Sonic Hedgehog Regulatory mutations |
| Syndactyly with metacarpal and metatarsal fusion | AD | HDX13 | |
| Metacarpal 4-5 fusion syndrome | XL | FGFI6 | Fibroblast growth factor 16 Regulatory mutations |
| Syndactyly with craniosynostosis (Philadelphia type) (Filippi syndrome) | AD | IHH | Indian Hedgehog Regulatory mutations |
| Syndactyly with microcephaly and mental retardation | AR | CKAP2L | Cytoskeleton associated protein 2-like |
| Meckel syndrome type 1,2,3,4,5,6 | AR | MKS1 | |
| | | TMEM216 | |
| | | TMEM67 | |
| | | CEP290 | |
| | | RPGRIP1L | |
| | | CC2D2A | |

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

### 42. Defects in joint formation and synostoses

| Condition | Inheritance | Gene/Mutation | Notes |
|-----------|-------------|---------------|-------|
| Multiple synostoses syndrome type 3 | AD | FGFI9 | FGFI9 |
| Proximal symphalangism type 1 | AD | NOG | Noggin |
| Proximal symphalangism type 2 | AD | GDF5 | Growth and Differentiation Factor 5 |
| Radio-ulnar synostosis with amegakaryocytic thrombocytopenia | AD | HOX11 | Homeobox A11 Regulatory mutations |
| Liebenberg syndrome | AD | PITX1 | Paired-like homeodomain transcription factor 1 |
| Congenital club foot | AD | PITX1 | Paired-like homeodomain transcription factor 1 Includes forms with polydactyly/limb malformations |

See also Spondylo-carpal-tarsal dysplasia; mesomelic dysplasia with Acral Synostoses; and others.
mountains of genetic information and look forward with curiosity to the tenth edition of the nosology.

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