European Commission

JRC - eurocat Central Registry

european surveillance of congenital anomalies

EUROCAT Syndrome Guide

Definition and Coding of Syndromes

Version July 2026

Joint Research

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The list of syndromes contained in the previous EUROCAT "Guide to the Coding of Eponyms and Syndromes" (Josephine Weatherall, 1979) was revised by Ingeborg Barisic, Helen Dolk, Ester Garne, Claude Stoll and Diana Wellesley at a meeting in London in November 2003. Approved by the members EUROCAT Coding & Classification Committee 2004: Ingeborg Barisic, Elisa Calzolari, Ester Garne, Annukka Ritvanen, Claude Stoll**,** Diana Wellesley

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TABLE OF CONTENTS

Introduction and Definitions 5
Coding Notes and Explanation of Guide 10
List of conditions to be coded in the syndrome field 12
List of conditions which should not be coded as syndromes 17

Syndromes – monogenic or unknown etiology
Aarskog syndrome 19
Acrocephalopolysyndactyly (all types) 20
Alagille syndrome 21
Alport syndrome 22
Angelman syndrome 23
Aniridia-Wilms tumor syndrome, WAGR 24
Apert syndrome 25
Bardet-Biedl syndrome 26
Beckwith-Wiedemann syndrome (EMG syndrome) 27
Blepharophimosis-ptosis syndrome 28
Branchiootorenal syndrome (Melnick-Fraser syndrome) 29
CHARGE syndrome 30
Cleidocranial dysplasia (dysostosis) 31
Cockayne syndrome 32
Cornelia de Lange syndrome (de Lange syndrome) 33
Crouzon syndrome 34
Dubowitz syndrome 35
Ehlers-Danlos syndrome 36
Fragile X syndrome 37
Fraser syndrome (cryptophthalmos-syndactyly) 38
Frontonasal dysplasia 39
Gorlin-Chaudhry-Moss syndrome 40
Hallermann-Streiff syndrome 41
Holt-Oram syndrome (heart-hand syndrome) 42
Hypoglossia-hypodactyly syndrome 43
Incontinentia pigmenti 44
Ivemark syndrome 45
Kartagener syndrome 46
Kaufman-McKusick syndrome 47
Klippel-Trénaunay-Weber syndrome (angioosteohypertrophy) 49
Larsen syndrome 50
Laurence-Moon syndrome 51
Lenz microphthalmos syndrome 52
Marfan syndrome 53
McCune-Albright syndrome 54
Meckel Gruber syndrome 55
Melnick-Needles syndrome 56
Miller-Dieker syndrome 57
Noonan syndrome 58
Orofacialdigital syndrome type 1 59

Orofacialdigital syndrome type 2 60
Otopalatodigital syndrome type 1 61
Otopalatodigital syndrome type 2 62
Pena-Shokeir syndrome 63
Pfeiffer syndrome 64
Popliteal pterygium syndrome 66
Prader-Willi syndrome 67
Robinow-Silverman-Smith syndrome 68
Rothmund-Thomson syndrome 69
Rubinstein-Taybi syndrome 70
Seckel syndrome 71
Silver-Russel syndrome 72
Sjögren-Larsson syndrome 73
Smith-Lemli-Opitz syndrome 74
Smith-Magenis syndrome 75
Sotos syndrome 76
Stickler syndrome 77
Sturge-Weber syndrome 78
TAR syndrome 79
Treacher-Collins syndrome (mandibulofacial dysostosis) 80
Trichorhinophalangeal syndrome 1 and 3 81
Van der Woude syndrome 82
Velocardiofacial syndrome/DiGeorge syndrome 83
Weaver syndrome 84
Weill Marchesani syndrome 85
Whistling face syndrome (Freeman-Sheldon syndrome) 86
Williams syndrome 87
Zellweger syndrome 88

Teratogenic syndromes
Fetal alcohol syndrome 90
Fetal cytomegalovirus syndrome 91
Fetal hydantoin syndrome 92
Fetal rubella syndrome 93
Fetal thalidomide syndrome 94
Fetal toxoplasmosis 95
Fetal valproate syndrome 96
Fetal warfarin syndrome 97
Fetal zika virus infection 98

Skeletal dysplasias
Achondrogenesis type 1A and type 1B 100
Achondrogenesis type 2 (incl. hypochondrogenesis) 101
Achondroplasia/hypochondroplasia 102
Acrodysostosis 103
Albers-Schönberg syndrome (osteopetrosis) 104
Camurati-Engelmann disease (diaphyseal dysplasia) 105
Chondrodysplasia punctata, rhizomelic, type 1 106
Chondrodysplasia punctata 2, X-linked 107

Diastrophic dysplasia 108
Ellis van Creveld syndrome 109
Enchondromatosis (incl. Maffucci syndrome, Ollier disease) 110
Jeune asphyxiating thoracic dystrophy 111
Kniest dysplasia 112
Metaphyseal chondrodysplasia 113
Metaphyseal dysplasia, Pyle syndrome 114
Metatropic dwarfism 115
Multiple congenital exostosis, diaphyseal aclasia 116
Nail patella syndrome (onycho-osteodysplasia) 117
Osteogenesis imperfecta type 118
Osteopoikilosis 119
Spondyloepiphyseal dysplasia congenita 120
Spondyloepiphyseal dysplasia tarda 121
Thanatophoric dysplasia 122

Associations
MURCS syndrome 124
Oculoauriculovertebral spectrum (Goldenhar) 125
VACTERL association 126

Sequences
Amniotic band sequence 128
Caudal regression sequence 129
Möebius sequence 130
Pierre-Robin sequence 131
Potter sequence 132
Prune-belly sequence 133
Sirenomelia 134
Klippel-Feil syndrome 48
Poland syndrome 65

INTRODUCTION AND DEFINITIONS

The Syndrome Guide is intended for use by EUROCAT congenital anomaly registries with a primary purpose of congenital anomaly surveillance and epidemiological research. The aim is to help the coders to code properly and with sufficient details rare genetic syndromes, skeletal dysplasias, associations and sequences. The list of syndromes concentrates on those which are mostly diagnosed in early infancy or prenatally, commonly associated with structural anomalies and/or found in the Q-chapter of ICD10/BPA. A future, on-line version could include additional rare conditions usually presenting at birth and associated with congenital anomalies.
In order to clarify terms that are commonly used to describe different patterns of associated anomalies, all definitions accepted and used by the EUROCAT network are included.

A **syndrome** (Greek σύνδρομον, meaning "going together") is a set of medical signs and symptoms that are correlated with each other. This term is used widely in different settings, sometimes closely related to pathogenesis and etiology of the disorder, and sometimes just describing a set of signs and symptoms not specific to only one disease. In the context of genetic disorders, we define a syndrome as a recognizable pattern of anomalies which are known or thought to be causally related (Opitz, 1994). In other words, a syndrome is a recognizable pattern of anomalies, causally but not necessarily pathogenetically related. Clinically, we define a syndrome based on the major characteristics of the entity. These can be major or minor anomalies and functional abnormalities, such as those affecting neurological, cognitive, sensory or behavioral functioning (Hennekam et al 2013). A syndrome can be caused by chromosomal abnormalities, contiguous gene deletions, single gene defects, or an environmental teratogen. Exceptionally, isolated anomalies may also be given a syndrome diagnosis when they have a single known cause (e.g. microcephaly due to X-ray exposure or congenital rubella syndrome with only cataracts).

Syndromes may include multiple anomaliess and/or sequences (see definition below). The anomalies and sequences are variably expressed in a syndrome, such that a given anomaly may be incompletely expressed or absent in certain individuals with the syndrome. Single anomalies that are unique to a syndrome, and that are always expressed in that syndrome, are very rare. Therefore, making the diagnosis of a syndrome depends on recognizing the overall pattern of the anomalies. In the more common syndromes, the frequency and range of expression of various anomalies and sequences are well known and are presented in this Guide.
Syndromes are often named after the physician or physicians that initially described the full clinical picture. Such eponyms are still in use, but there has been a shift towards naming conditions descriptively by symptoms or underlying cause (e.g. mandibulofacial dysostosis and not Treacher Collins syndrome). As the eponymous syndrome names often persist in common usage, the Syndrome Guide includes all known terms for the specific disorder, thus facilitating the coders to find quickly the appropriate codes in the on-line version of the Guide.

It is important to note that many so-called "syndromes" are not syndromes according to current clinical genetics consensus and EUROCAT definition. This Guide can be used to help recognize which conditions with "syndrome" in their name should not be considered

real syndromes and instead be coded under the malformation fields.

EUROCAT codes syndrome diagnoses as a special variable allowing their separate recognition and analysis as a single entity in spite of the presence of a set of associated features. The EUROCAT recommended variable set allows for the coding of one syndrome and eight anomalies, but additional information should be placed in the text format. It is important ALWAYS to also give a text description of the syndrome. All major anomalies should be coded and minor anomalies should be coded with minor codes only. If there is no code, describe the the minor anomaly using written text. If the syndrome is diagnosed but no major anomaly present, please give syndrome name in the syndrome variable, and note in the first malformation variable that only minor anomalies/dysmorphic features are present (Q18.9).

The purpose of the guide is to facilitate surveillance, clinical and epidemiological research in the field of rare genetic syndromes. Therefore, we advise giving as much detail as possible in describing clinical features, including minor anomalies and other characteristic features.

The International Classification of Disease version 10 (ICD10) with British Paediatric Association (BPA) extension specifies the coding of a range of syndromes. This Guide can be used as a help to find the appropriate codes.

The Online Mendelian Inheritance in Man (OMIM) 6-digit codes (website https://www.ncbi.nlm.nih.gov/omim) can be used as well (in the "McKusick" variable). OMIM codes should never replace specific ICD10/BPA coding.

In addition, ORPHA numbers are increasingly in use and are therefore added to the syndrome list (http://www.orpha.net). The present versions of ECD and EDMP have no defined variable for use of the ORPHA number, but the Coding Committee recommends introducing ORPHA number in the malf8 variable starting with one letter and up to 6 digits in the waiting time for the updating of EDMP (Coding & Classification Committee, December 2016).

It is recommended that all coding of syndromes should be done by a medical geneticist, especially when using the ORPHA numbers and OMIM codes as it requires more knowledge of differential diagnosis, family history and genetic tests.

If we observe a pattern of anomalies, at least two of which are morphologic, that occur often together, and where a causal relationship has not been identified, a condition may be referred to as an **association** (Hennekam et al 2013). By definition, an association indicates that the collection of signs and symptoms occurs in combination more frequently than would be likely by chance alone. Opitz (1994) defines association as an idiopathic (i.e. cause unknown) pattern of multiple anomalies arising during blastogenesis. Examples: VACTERL (Vertebral, Anal, Cardiac, TE fistula, Renal, Limb defects) and MURCS (Mullerian duct aplasia, Renal aplasia, Cervical Somite dysplasia). Some conditions previously classified as associations were later found to be monogenic syndromes (e.g. CHARGE). For practical purposes, there are only three well known associations given in this Guide. Although associations do not have a presumed single cause, EUROCAT recommends they be coded in the syndrome variable. Please use the

recommended codes only, so that they can be easily distinguished and separated from syndromes and ALWAYS give the name in text. Genetic expertise is also welcomed here and it is recommended that registries only code an association if the baby has been seen by a clinician who has named the association. Registries should not code an association on the basis of a certain combination of anomalies or anomaly codes that are present in the registry records, since this can compound recording error and in any case can easily, if required, be done by computer at a later stage.

Associations will not usually be treated in EUROCAT epidemiological analyses as equivalent to syndromes, as there is by definition no known aetiology. They are of interest for epidemiological surveillance as they may indicate an association with a specific teratogen or may be indicators of disruption of developmental pathways of interest for the researchers. They will usually be grouped as multiple congenital anomalies, not syndromes, but deserve special consideration.

A **sequence** occurs when a single developmental defect results in a chain of secondary defects, which may, in turn, lead to tertiary defects. The result is a variably expressed group of defects, all of which can be traced back to the original event. The EUROCAT recommended definition of a sequence is a "pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor" (Spranger, 1982). For example, the primary defect in Pierre Robin syndrome is mandibular hypoplasia, which results in posterior displacement of the tongue, which precludes closure of the palatal arches. "A myelomeningocele may lead to lower limb paralysis, muscle wasting, clubfeet, incontinence, urinary tract infection and renal damage, constipation and dilatation of the bowel etc. The pattern is called the meningomyelocele sequence". Furthermore, "a sequence is a pathogenic and not a causal concept" – there may be many initial causes for the same cascade of defects (Spranger, 1982). A malformation, dysplasia, deformation, disruption or mechanical factor may give rise to a cascade of secondary problems in subsequent morphogenesis. In epidemiologic analysis relating to risk, a spina bifida with a clubfoot is the same entity as a spina bifida without a clubfoot. Both single anomalies and sequences may occur in isolation, or as part of a group of anomalies.

All component anomalies of syndromes, associations, and sequences should be coded. This is to facilitate reclassification where required in the future, and also to avoid spurious differences in the prevalence of individual anomalies between registries. For example, omphalocele is a frequent component of trisomy 18 syndrome, and trisomy 18 is associated with a large proportion of omphalocele cases. The total prevalence of omphalocele should be calculable including cases which are part of syndromes as well.

In the context of classification of the congenital anomalies it is also important to differentiate primary abnormalities of the structure of an organ or a part of an organ that can be traced back to an anomaly of its development (e. g. congenital heart defect) from secondary anomalies due to **disruption** - interruption of the normal development of an organ that can be traced back to outer influences, either teratogenic agents (infection, chemical substance, ionizing radiation) or a trauma (amniotic bands, which led to an amputation). The most widespread infectious agents are the Cytomegalo virus and the toxoplasmosis parasite (Toxoplasma gondii). To the chemical, teratogenic agents belong among others, thalidomide, warfarin, and various antiepileptics.

Deformation is an altered shape or position of a body part that occurs due to outer mechanical effects on existing normal organs or structures (e.g. deformation of the foot due to oligohydramnios). **Dysplasia** is a morphologic anomaly arising either prenatally or postnatally from dynamic or ongoing alteration of cellular constitution, tissue organization or function within a specific organ or a specific tissue type. (e.g., hemihyperplasia) (Hennekam et al 2013). Numerous dysplasias are genetically caused, and usually due to single gene mutation, but may be also secondary to teratogenic exposure. **Agenesis** is the absence of an organ due to a development that failed to happen during the embryonic period. If incomplete, than the term hypoplasia is used.

Skeletal Dysplasias and other Disorders of Skeletal Development

The skeletal dysplasias (osteochondrodysplasias) are a heterogeneous group of more than 350 disorders associated with a generalized abnormality of the skeleton. Although each skeletal dysplasia is relatively rare, collectively the birth incidence of these disorders is almost 1/5000.

Generalized disorders of cartilage and bone have been referred to as **skeletal dysplasias**, whereas those that affect an individual bone or group of bones have been referred to as **dysostoses**. Dysostoses are manifestations of transient signalling defects in the skeleton during organogenesis. They are finite, because of the transient nature of the defective process, usually due to genes that are active during embryogenesis for a limited period of time. They may occur singly or in combination, or as part of pleiotropic disorders if the controlling gene is expressed in many organs. Dysostoses are often part of a specific syndrome (examples: Holt-Oram syndrome, acrocephalopolysyndactyly etc). **Dysplasias** are defects of prenatally expressed genes that continue to be expressed in postnatal life. These genes are mostly not expressed during organogenesis (as in dysostoses).

The skeletal dysplasias are associated with abnormalities in the patterning, development, maintenance, and size of the appendicular and axial skeleton and frequently result in disproportionate short stature. They result from mutations in various families of genes that encode extracellular matrix proteins, transcription factors, tumour suppressors, signal transducers (ligands, receptors, and channel proteins), enzymes, cellular transporters, chaperones, intracellular binding proteins, RNA processing molecules, cilia and cytoplasmic proteins, and a number of gene products of currently unknown function. The skeletal dysplasias are included as a group in the Q chapter and the most common ones, that have their own ICD10/BPA code, are included in the Syndrome Guide. As many of them are known under their eponyms as syndromes (e.g. Jeune syndrome, Maffucci syndrome, Ellis van Creveld syndrome etc.) they are listed separately in this guide to help them to be found for coding.

We recognise that there is no complete consensus about definitions, nor about which conditions belong to which definition. It is essential to code specifically and consistently, giving maximum text information, to allow reclassification as knowledge and consensus changes.

References

1. Carey JC et al **(2009)**, Special Issue: Elements of Morphology: Standard Terminology, American Journal of Medical Genetics, Vol, 149A, pp 1–127
2. Hennekam RC, Biesecker LG, Allanson JE, Hall JG, Opitz JM, Temple IK, Carey JC; Elements of Morphology Consortium **(2013)**, Elements of morphology: general terms for congenital anomalies. American Journal of Medical Genetics, Vol, 161A, pp 2726-33.
3. Opitz JM **(1994)**, "Association and Syndromes: Terminology in Clinical genetics and Birth Defects Epidemiology: Comments on Khoury Moore and Evans", American Journal of Medical Genetics, Vol 49, pp 14-20.
4. Spranger J, Benirschke K, Hall JG, Lenz W, Lowry RD, Opitz JM, Pinsky L, Scharzacher HG, Smith DW **(1982)**, "Errors of Morphogenesis: Concepts and Terms", Journal of Paediatrics, Vol 100, pp 160-165.

Coding Notes and Explanation of Guide

1. In Table 1, the first coding column gives the ICD10/BPA codes. ICD10/BPA is available on the EUROCAT website and should be in routine use by all registries. If the ICD10/BPA code is the same for more than one syndrome, the code is annotated as "not specific" (in italics) and special care should be given to the text description.

2. The second coding column gives the ICD9 code, with BPA extension (5th digit), and with the old EUROCAT 6th digit (Weatherall, 1979). This is to enable this guide to be used for the analysis of past years of data.
Warning:

a) Especially where fewer than the full 6 digits are used, these codes may not be specific to a single syndrome

b) Care should be given interpreting a zero sixth digit as a specific code extension, rather than as a "filling" digit. Analysis of data using ICD9 based codes should use text information and refer to the original ICD9 and BPA codebooks.

3. The third column gives the usual OMIM code, where the condition has Mendelian inheritance. Where there are several OMIM codes for the same syndrome, a qualified medical geneticist must determine which code is the most appropriate for the particular case – the various codes are not simple alternatives for the same condition. An OMIM code should only be given where there is sufficient evidence for a precise diagnosis.

4. The fourth column gives the ORPHA number. This number is applicable to all rare diseases (i.e. also available for teratogenic syndromes). As for the OMIM codes, it is advised that in case of several available numbers the medical geneticist decides which number is the most appropriate.

5. Table 2 gives conditions which should NOT be coded as syndromes. Code within the malformation fields, giving full text information.

6. All component anomalies of syndromes, associations and sequences should be coded. Where the same code is given both to a syndrome/association/sequence diagnosis and to one of its component anomalies, it is recommended to use this code twice where necessary, with an explanation given in the text descriptions.

7. In the case of both a diagnosed syndrome and a microdeletion or microduplication, code both the syndrome (see syndrome list) and give the code for the microdeletion (Q935 - other deletions of part of a chromosome) or microduplication (Q923 - minor partial trisomy). Give the microdeletion/microduplication description in the karyotype text following the recommendations in Guide 1.5 and the syndrome name in the syndrome text. The most common syndromes with a microdeletion are Di George/velocardiofacial (microdeletion 22q11.2), Prader Willi (15q11-q13 pat), Angelman (15q11-13, mat), Williams (7q11.23), MillerDieker (17p13.3), Alagille (20p12), Smith Magenis (17p11.2), WAGR-Aniridia Wilms (11p13), TAR (1p21), Rubinstein Taybi (16p13), Sotos (5q35), 1p36 deletion. Many new small deletions and duplications have been discovered using new technologies such as chromosome microarray (CMA). Their clinical presentation is well known and already accurately described. At present they are not included in the Syndrome Guide.

8. Where a syndrome cannot be found in the Table 1, the code for "other specified syndromes" can be used (Q878) with the name of the syndrome in text.

9. Where there are two syndromes coincidentally present in the same baby, code the second syndrome in the first malformation field, with text description.

10. When using the EUROCAT database for all years from 1980, be aware that the McKusick code for earlier years was a 5 digit code.

11. For congenital infections (e.g. Rubella, CMV) and other exogenous syndromes (e.g. Valproate embryopathy) include only syndromes due to early pregnancy exposure with major anomalies. Code all component malformation.

12. SKELETAL DYSPLASIA. If a final diagnosis of a lethal or severe skeletal dysplasia is not possible, as in TOPFA or neonatal deaths without *post mortem* examination, use the code Q788. For late diagnosed unspecified skeletal dysplasias use Q789. Coding tip issued by Coding Committee, August 2007.

13. For each entry there is a one-page description that includes all names/eponyms of the condition, a short definition, associated major congenital anomalies, dysmorphic features/minor anomalies and a list of other characteristic signs and symptoms. The list of signs and symptoms is not exhaustive and some features not listed may be present in patient as well. The most distinctive features (major features) of the syndrome are marked in red. This enables the coder to check quickly if they have received enough data to support the diagnosis of the syndrome (e.g. it is not sufficient to write in the syndrome field Beckwith Wiedemann syndrome - in the malformation fields and in the text description there should be enough data to support the diagnosis). Note that EUROCAT is committed to research in the field of rare diseases, and that for this purpose we need not only epidemiological data but also detailed clinical description and data on genetic testing. We hope that this quick overview of selected rare conditions in the Syndrome Guide will facilitate collection and coding of data on rare diseases included in the Q chapter. It is planned to make this guide more user-friendly with on-line easy access and search facilities.

Table 1. List of conditions to be coded in the syndrome field. Updated on 23-6-2026 by the EUROCAT coding and classification committee[#]

	ICD10-BPA[*]	ICD9-BPA[*^]	OMIM	ORPHA
Syndromes				
Aarskog syndrome	Q8710	*75989*	305400, 100050	915
Acrocephalopolysyndactyly (all types)	Q8700	755501	201000, 201020, 101120	65759, 65798,
Aicardi syndrome	*Q878*		304050	50
Alagille syndrome	Q4471	*75167*	118450, 610205	52, 26100, 261619, 261629
Alport syndrome	Q8780	759870	104200, 203780, 301050	63, 88918, 88919, 88917
Angelman syndrome	Q8785	*759899*	105830	72
Apert syndrome (acrocephalosyndactyly)	Q8701	*755500/02*	101200	87
Axenfeld-Rieger syndrome	*Q878*		180500, 602482, 601499	782
Baere Stevenson cutis gyrata syndrome	*Q878*		123790	1555
Bardet-Biedl syndrome	Q8781	759820	209900	110
Beals syndrome	*Q875*		121050	115
Beckwith-Wiedemann syndrome (EMG syndrome)	Q8730	759874	130650	116
Blepharophimosis-ptosis syndrome	*Q878*	74360	110100	126
Branchiootorenal syndrome (BOR syndrome)	*Q878*	*75989*	113650, 610896	107
Cardiofaciocutaneous syndrome	*Q878*		115150 + several	1340
Cat-eye syndrome	*Q928*		115470	195
Cerebrocostomandibular syndrome	*Q878*		117650	1393
CHARGE syndrome	*Q878*	*75989*	214800	138
Cleidocranial dysplasia (dysostosis)	Q7402	755551	119600, 216330	1452
Cockayne syndrome	Q8711	759826	133540, 214150 216400, 216411 278780, 610756 610758, 616570	191, 90321, 90322, 90324
Cornelia de Lange syndrome (de Lange syndrome)	Q8712	759821	122470, 300590, 300882, 610759, 614701	199
Costello syndrome	*Q878*		218040	3071
Cri-du-chat syndrome (5p deletion)	Q934	123450	123450 + several	281
Crouzon syndrome	Q751	75601	123500	207
De Grouchy syndrome type 1 (18p-syndrome)	*Q935*		146390	1598
De Grouchy syndrome type 2 (18q-syndrome)	*Q935*		601808	1600
Dubowitz syndrome	Q8713	*75989*	223370	235
Ehlers-Danlos syndrome	Q796	75685	130000 + several	287 + several
Fanconi anemia	D610& Q878		227650 + several	84
Fragile X syndrome	Q992	75983	300624	908
Fraser syndrome (cryptophthalmos-syndactyly)	*Q8702*	*759892*	219000	2052
Frontonasal dysplasia	Q7581	*75400*	136760	391474
Fryns syndrome	*Q878*		229850	2059

Gorlin-Chaudhry-Moss syndrome (craniofacial dysostosis-genital, dental, cardiac anomalies syndrome)	*Q878*	*759898*	233500	2095
Greig cephalopolysyndactyly syndrome	*Q870*		175700	380
Hallermann-Streiff syndrome (oculomandibulofacial syndrome)	Q8705	756050	234100	2108
Holt-Oram syndrome (heart-hand syndrome)	Q8720	759842	142900	392
Hydrolethalus	*Q878*		236680	2189
Hypoglossia-Hypodactylia syndrome	*Q878*	*759846*	103300	989
Ivemark syndrome	*Q878*	*75989*	208530	97548
Joubert syndrome	*Q878*		610188, 08629 + several	475
Kabuki syndrome	*Q870*		147920	2322
Kartagener syndrome	Q8934	759340	244400	98861
Kaufman-McKusick syndrome	*Q878*	*75248*	236700	2473
Klinefelter syndrome	Q980, Q981, Q984			
Klippel-Trenaunay (-Weber) syndrome (angioosteohypertrophy)	Q8721	759840	149000, 608355	2346
Larsen syndrome	Q7484	75581	150250, 245600	503, 284139
Laurence-Moon syndrome	Q8781	759822	245800	2377
Lenz microphthalmos syndrome	*Q878*	*74310*	309800	568
LEOPARD syndrome / Noonan syndrome with multiple lentigines	*Q871*		151100, 611554, 613707	500
Loeys-Dietz syndrome	*Q875*		609192, 610168 + several	60030
Marfan syndrome	Q874	759860	154700, 610168	558
McCune-Albright syndrome	Q781	756512	174800	562
Meckel Gruber syndrome	Q6190	*75989*	249000 + several	564
Melnick-Needles syndrome	*Q778*	*759845*	309350	2484
Miller-Dieker syndrome	*Q878*	*74224*	247200	531
Muenke syndrome	Q870		602849	53271
Nager syndrome (Mandibulofacial dysostosis with preaxial limb anomalies)	Q754		154400	245
Neurofibromatosis type 1 (von Recklinghausen disease)	Q850		162200	636
Noonan syndrome	Q8714	759896	163950 + several	648
Opitz GBBB syndrome	*Q878*		300000	2745
Orofacialdigital syndrome type 1	Q8707	759802	311200	2750
Orofacialdigital syndrome type 2	Q8707	759802	252100	2751
Otopalatodigital syndrome type 1	*Q870F*	759845	311300	669, 90650
Otopalatodigital syndrome type 2	*Q870F*	759845	304120	669, 90652
Pena-Shokeir syndrome	Q870E	*75989*	208150, 300073	994
Pfeiffer syndrome	*Q878*	755501	101600	710
PIK3CA-related overgrowth spectrum	*Q873*		613089, 612918, 155500, 602501	168984, 140944, 295044, 295047, 60040, and others
Popliteal pterygium syndrome	*Q878*	*756885*	119500, 263650	1300, 1234
Prader-Willi syndrome	Q8715	759872	176270, 615547	739
Proteus syndrome	*Q873*		176920	744
Roberts syndrome	*Q878*		268300	3103
Robinow-Silverman-Smith syndrome	Q8716	*75989*	180700, 268310	97360, 3107, 1507

Rothmund-Thomson syndrome	*Q878*	*757303*	268400	2909
Rubinstein-Taybi syndrome	*Q8723*	759841	180849, 610543, 613684	783, 353281, 353284
Seckel syndrome	Q8718	759827	210600 + several	808
Silver-Russel syndrome	Q8717	759823	180860, 312780	813
Sjögren-Larsson syndrome	Q871A	75712	270200	816
Smith-Lemli-Opitz syndrome	Q8719	759828	270400	818
Smith-Magenis syndrome	*Q878*	*75989*	182290	819
Sotos syndrome	Q8731	756883	117550, 617169	821
Stickler syndrome	Q8709	*75989*	108300, 604841, 184840	828, 90653, 90654, 166100
Sturge-Weber syndrome	Q8581	759611	185300	3205
TAR syndrome (thrombocytopenia-absent radius syndrome)	Q8725	*75526*	274000	3320
Townes-Brocks syndrome	*Q878*		107480, 617466	857
Treacher-Collins syndrome (mandibulofacial dysostosis)	Q754/Q870A	756041	154500, 248390, 613717	861
Trichorhinophalangeal syndrome	*Q870B*	*75989*	190350, 190351	77258
Triploidy or polyploidy	Q927		-	3376
Trisomy 13 (Patau syndrome)	Q914-Q917		-	3378
Trisomy 18 (Edwards syndrome)	Q910-Q913		-	3380
Trisomy 21 (Down syndrome)	Q900-Q902, Q909		190685	870
Tuberous sclerosis (Bourneville syndrome)	Q851		191100, 613254	805
Turner syndrome	Q960-Q964, Q968, Q969		-	881
Van der Woude syndrome	*Q878*	*75989*	119300, 604547, 606713	888
Velocardiofacial syndrome/DiGeorge syndrome/22q11 deletion syndrome	D821	27910	188400, 192430	567
WAGR (Wilms tumor-aniridia-genitourinary anomalies-intellectual disability syndrome)	*Q878*		194072, 612469	893
Weaver syndrome	Q8732	*75989*	277590	3447
Weill Marchesani syndrome	*Q875*	*75989*	277600, 608328, 614819	3449
Whistling face syndrome (Freeman-Sheldon syndrome)	Q870C	759807	193700, 277720, 616266	2053
Williams syndrome	Q8784	*75989*	194050	904
Wolff-Hirschhorn syndrome (deletion 4p)	Q933		194190	280
Zellweger syndrome	Q8783	759875	214100 + several	912
Teratogenic syndromes				
Fetal alcohol syndrome	Q860	76076	-	1915
Fetal cytomegalovirus (CMV) syndrome	P351	77110	-	294
Fetal hydantoin syndrome	Q861	*76070*	-	1912
Fetal rubella syndrome	P350	77100	-	290
Fetal thalidomide syndrome	Q8682	7607	-	3312
Fetal toxoplasmosis	P371	77121	-	858
Fetal valproate syndrome	Q868	7607	-	1906
Fetal warfarin syndrome	Q862	7607	-	1914
Fetal zika syndrome	P354	-	-	448237

Skeletal dysplasias				
Achondrogenesis type 1A and type 1B	Q7700	*75644*	200600, 600972	932, 93299, 93298
Achondrogenesis type 2 (incl. hypochondrogenesis)	Q7701/ Q7702	*75644*	200610	93296/93297
Achondroplasia/hypochondroplasia	Q774	75643	100800	15
Acrodysostosis	*Q778*	*75658*	101800	950
Albers-Schönberg syndrome (osteopetrosis)	Q782	756540	166600	53
Campomelic dysplasia	*Q871*		114290	140
Camurati-Engelmann disease (diaphyseal dysplasia)	Q783	756551	131300	1328
Chondrodysplasia punctata, rhizomelic, type 1	Q773	*75644*	215100	177
Chondrodysplasia punctata 2, X-linked	Q773	*75644*	302960	35173
Diastrophic dysplasia	Q775	756441	222600	628
Ellis van Creveld syndrome	Q776	75652	225500, 617088	289
Enchondromatosis (including Maffucci)	Q784/ Q7840	75641/75642	166000, 614569	296, 163634
Jarcho-Levin syndrome	*Q779*		277300 + several	2311
Jeune asphyxiating thoracic dystrophy	Q772	75640	208500 + several	474
Kniest dysplasia	*Q778*	*75658*	156550	485
Leri-Weill dyschondrosteosis	*Q778*		127300	240
Metaphyseal chondrodysplasia	Q7781	75645	156400	33067
Metaphyseal dysplasia, Pyle syndrome	Q785	75655	265900	3005
Metatropic dysplasia	Q7780	756442	156530	2635
Multiple congenital exostosis, diaphyseal aclasia	Q786	75657	133700, 133701, 600209	321,
Nail patella syndrome (onycho-osteodysplasia)	Q8722	75683	161200	2614
Osteogenesis imperfecta	Q7800	75650	166200, 166210, 166220, 166230, 259420, 259440, 610682, 610915, 610967, 610968, 613848, 613849, 613982, 614856, 615066, 615220, 616229, 616507	666, 216796, 216804, 216812, 216820, 216828
Osteogenesis imperfecta type 1 (tarda)	*Q7808*		166200	216796
Osteopoikilosis	Q7880	75656	166700	1306
Spondyloepiphyseal dysplasia congenita	Q777	*75646*	183900	94068
Spondyloepiphyseal dysplasia tarda	Q777	75646	313400	93284
Thanatophoric dysplasia	Q771	*756443*	187600, 187601	2655, 1860, 93274
Hereditary skin disorders				
Ectodermal dysplasia, anhidroditic/hypohidrotic	Q824		129490, 224900, 305100, 614940, 614941	238468
Ectodermal dysplasia, hidrotic	Q8282		129500	189
EEC syndrome	Q824		604292	1896
Epidermolysis bullosa dystrophica	Q812		131750, 226600 + several	303
Epidermolysis bullosa letalis (Herlitz' syndrome)	Q811	757.33	226700	79404
Epidermolysis bullosa simplex	Q810		131760 + several	304

Epidermolytic hyperkeratosis (congenital bullous ichthyosiform erythroderma)	Q803		113800, 620150, 620148, 607602	312, 281139
Harlequin fetus/icthyosis	Q804		242500	457
Hereditary lymphoedema (Milroy disease)	Q820		153100, 611944	79452
Hypomelanosis of Ito	Q8283		300337	
Ichthyosis vulgaris	Q800		146700	
Incontinentia pigmenti	Q823	75735	308300	464
Lamellar ichthyosis (non-bullous ichthyosiform erythroderma)	Q802		242300, 601277, 604777, 606545, 612281, 613943, 146750, 617574, 617571	313
Mastocytosis (urticaria pigmentosa)	Q822		154800	98292
Xeroderma pigmentosa	Q821		278700, 278720, 278730, 278740, 278760, 278780, 610651	910
X-linked ichthyosis	Q801		308100	461
Associations				
MURCS syndrome	*Q518*	*75249*	601076	2578
Oculoauriculovertebral spectrum (Goldenhar syndrome)	Q8704	75606	164210	374
VACTERL association	Q8726	759895	192350	887
OEIS complex	*Q6410*		258040	93929
Pentalogy of Cantrell	*Q897*		313850	1335

* codes printed in *italics* are not specific to the syndrome listed
^ the ICD9-BPA codes were not updated in 2026, because they are no longer in use
# Please note that this table is not exhaustive and will be revised periodically by the EUROCAT coding and classification committee. In line with EUROCAT's primary objective of congenital anomaly surveillance, the list prioritizes syndromes that are easily recognizable in infancy and which are often associated with major structural congenital anomalies.

Table 2. List of conditions which should not be coded as syndromes (code as as MALFO variable)

	ICD10-BPA*	ICD9-BPA*^	OMIM	ORPHA
Sequences				
Amniotic band sequence	Q7980	*75688*	217100	1034
Caudal regression sequence	Q8980	*75989*	600145	3027
Möebius sequence	Q8706	3568	157900	570
Pierre-Robin sequence	Q8708	75603	261800	718
Potter sequence	Q606	753000	191830	1848
Prune-belly sequence	Q794	75672	100100	2970
Sirenomelia	Q8724	759844	600145	3169
Anomalies with syndrome names but not a syndrome				
Apple peel syndrome	Q411	*75111*	-	-
Arnold-Chiari syndrome	Q070	74288	118420, 207950	268882, 1136
Arthrogryposis multiplex congenita	Q743	*75688*	208100	1037
Congenital blind loop syndrome	Q438	*75119*	-	-
Conjoined twins	Q894	75949	-	-
Constriction ring syndrome of upper limb NOS	*Q719*	75558	217100	295000
Constriction ring syndrome of lower limb NOS	*Q729*	*75568*	217100	295000
Cryptophthalmos syndrome (isolated cryptophtalmos)	*Q112*	*74380*	123570	91396
Cyclops syndrome	Q8703	*75989*	-	-
Dandy-Walker syndrome/anomaly	Q031	742.31	220200	217
Eisenmenger syndrome	Q2181	745.41	-	97214
Hirschsprung syndrome/disease	Q431	751.30	142623	388
Hypoplastic left heart syndrome	Q234	746.70	241550, 614435	2248
Hypoplastic right heart syndrome	Q226	*74688*	-	98723
Klippel-Feil syndrome	Q761	756110	118100, 214300, 613702	2345
Lutembacher syndrome (ASD+mitral stenosis)	Q2114	74552	-	-
Marcus Gunn syndrome/phenomenon	Q0780	74280	154600	91412
Megacystis-megaureter syndrome/sequence	Q6476	75322	-	238637
Poland syndrome	Q7982	75680	173800	2911
Scimitar syndrome	Q268	74743	608281	185
Small left colon syndrome	Q432	75152	-	-
Taussig-Bing syndrome	Q201	74511	-	99045

* codes printed in *italics* are not specific to the syndrome listed

^ the ICD9-BPA codes were not updated in 2026, because they are no longer in use

Syndromes – monogenic or unknown etiology

Name: Aarskog syndrome

Synonyms:

Aarskog - Scott syndrome
Faciodigitogenital syndrome
Faciogenital dysplasia

ICD 10 – BPA code	Q8710
ICD 9 – BPA-E*	*75989*
OMIM code	305400; 100050
ORPHA number	ORPHA915

Aarskog syndrome is characterized by mild short stature, distinctive facial features (widow's peak, round face, hypertelorism, ptosis, transverse crease below the lower lip), small hands and feet and genital anomalies (shawl scrotum, cryptorchidism).

Associated major congenital anomalies

HEAD AND NECK
- Ptosis
- Cleft lip/palate

CARDOVASCULAR
- Congenital heart defect (ventricular septal defect)

GENITOURINARY
- Hypospadias

SKELETAL
- Brachydactyly
- Camptodactyly

Dysmorphic features/minor anomalies

- Widow's peak, frontal cowlick
- Broad forehead
- Hypertelorism, downslanting palpebral fissures
- Low set ears, fleshy earlobes
- Maxillary hypoplasia
- Broad nasal bridge, small/short nose, anteverted nostrils
- Wide philtrum
- Transverse crease below the lower lip
- Umbilicus of abnormal shape and position
- Clinodactyly of the 5th finger
- Syndactyly (usually mild and classified as minor)
- Hypermobile fingers
- Inguinal hernia
- Shawl /overriding scrotum
- Cryptorchidism

Other

- Acromelic short stature (mild, postnatal)
- Developmental delay/intellectual disability

Genetic test

Detection of the pathogenic variants in the faciogenital dysplasia gene (*FGD1*) (Xp11.22)

Name: Acrocephalopolysyndactyly
(all types excl. type 5, Pfeiffer syndrome)

Synonyms:
Acrocephalopolysyndactyly type 2 (Carpenter)
Acrocephalopolysyndactyly type 3 (Sakati-Nyhan-Tysdale)
Acrocephalopolysyndactyly type 4 (Goodman)

ICD 10 – BPA code	Q8700
ICD 9 – BPA-E*	755501
OMIM code	201000; 101120; 201020,
ORPHA number	ORPHA65759; ORPHA65798

Acrocephalopolysyndactyly type 2 is characterized by pre-axial polydactyly of the feet in conjunction with craniosynostosis. There is brachydactyly and syndactyly of hands Acrocephalopolysyndactyly type 3 and 4 are considered to be within the clinical spectrum of Carpenter syndrome.

Associated major congenital anomalies

CARDIOVASCULAR
- Atrial septal defect
- Ventricular septal defect
- Pulmonic stenosis
- Tetralogy of Fallot
- Transposition of great vessels
- Patent ductus arteriosus

ABDOMEN
- Omphalocele
- Accessory spleens

GENITOURINARY
- Hydronephrosis

SKELETAL
- Craniosynostosis (coronal, sagittal, lambdoid sutures)
- Scoliosis
- Absent coccyx
- Brachydactyly
- Aplasia or hypoplasia of the middle phalanges
- Postaxial polydactyly
- Syndactyly
- Camptodactyly

Dysmorphic features/minor anomalies

- Acro/brachycephaly
- High forehead
- Midface hypoplasia
- Low-set, malformed ears, preauricular pits
- Bilateral ptosis, occasionally proptosis
- Prolonged retention of primary teeth, hypodontia
- Umbilical hernia
- Pilonidal sinus
- Clinodactyly of the 5th finger
- Spina bifida occulta
- Cryptorchidism

Other

- Conductive/ sensorineural hearing loss
- Variable developmental delay/intellectual disability
- Precocious puberty
- Short stature
- Obesity

Genetic test

Detection of pathogenic variants in the Ras-associated protein *RAB23* gene (6p11)

Name: Alagille syndrome

Synonyms:

Alagille-Watson syndrome
Arteriohepatic dysplasia
Syndromic bile duct paucity
Cholestasis with peripheral pulmonary stenosis
Hepatic ductular hypoplasia, syndromic

ICD 10 – BPA code	Q4471
ICD 9 – BPA-E*	*75167*
OMIM code	118450; 610205
ORPHA number	ORPHA52; ORPHA261600 (del 20p12), ORPHA261619(*JAG1*), ORPHA261629 (*NOTCH2)*

Alagille syndrome is a multisystem disorder involving primarily the liver, heart, eyes, face, and skeleton. The major clinical manifestations are cholestasis, characterized by bile duct paucity on liver biopsy, congenital cardiac defects, primarily involving the pulmonary arteries, posterior embryotoxon in the eye, typical facial features, and butterfly vertebrae. Renal and central nervous abnormalities also occur.

Associated major congenital anomalies

HEAD AND NECK
- Posterior embryotoxon
- Cataracts
- Anterior chamber anomalies
- Microcornea

CARDIOVASCULAR
- Atrial septal defect
- Pulmonic stenosis
- Tetrology of Fallot
- Ventricular septal defect
- Coarctation of aorta

GENITOURINARY
- Small kidneys
- Cystic kidneys

SKELETAL
- Vertebral anomalies (butterfly vertebrae)
- Hemivertebrae
- Short ulnae
- Short distal phalanges

Dysmorphic features/minor anomalies

- Broad forehead
- Triangular face
- Hypertelorism, upslanting palpebral fissures, deep-set eyes
- Long nose, bulbous tip
- Pointed chin
- Peripheral pulmonary artery stenosis
- Vesicoureteral reflux

Other

- Bile duct paucity, cholestatic liver disease, cirrhosis
- Hepatocellular carcinoma, papillary thyroid carcinoma
- Pancreatic insufficiency
- Renal tubular acidosis, renal insufficiency
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants or deletions in *JAG1* (about 94%-96% of cases) (20p12) or in *NOTCH2* (1%-2% of cases)(1p12)

Name: Alport syndrome
Synonyms:
Alport deafness-nephropathy

ICD 10 – BPA code	Q8780
ICD 9 – BPA-E*	759870
OMIM code	104200; 203780; 301050
ORPHA number	ORPHA63; 88918, 88919; 88917

Alport syndrome is an inherited disease characterised by glomerular nephropathy with hematuria, progressing to end-stage renal disease, associated with cochlear and ocular involvement.

Associated major congenital anomalies

Dysmorphic features/minor anomalies

Other

- Glomerulonephropathy leading to renal failure
- Progressive sensorineural hearing loss, especially affecting high frequencies (developing in late childhood or early adolescence)
- Anterior lenticonus, lens opacities, cataracts, myopia, perimacular flecks, corneal endothelial vesicles, corneal erosions
- Hypertension

Genetic test

Detection of pathogenic variants in the:

- Collagen, type IV, alpha-3 gene (*COL4A3*)(104200) (2q36.3)
- Collagen, type IV, alpha-3 gene (*COL4A3*)(203780) (2q36.3)
- Collagen, type IV, alpha-4 gene (*COL4A4*) (203780) (2q36.3)
- Collagen, type IV, alpha-5 gene (*COL4A5*) (301050) (Xq22.3)

Name: Angelman syndrome
Synonyms:
Happy puppet syndrome

ICD 10 – BPA code	Q8785
ICD 9 – BPA-E*	*759899*
OMIM code	105830
ORPHA number	ORPHA72

Angelman syndrome is characterized by severe intellectual and developmental disability, movement or balance disorder, seizures, jerky movements (especially hand-flapping), frequent laughter or smiling, and sleep disturbance.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly (postnatal)

SKELETAL
- Scoliosis (postnatal)

Dysmorphic features/minor anomalies

- Macrostomia, protruding tongue, wide-spaced teeth
- Prognathia (in adulthood)

Other

- Feeding diffculites, drolling
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs
- Frequent laughter/smiling, hand flapping movements; hypermotoric behavior, short attention span
- Seizures, onset usually < 3 years of age, abnormal EEG, chracteristic pattern with large amplitude slow-spike waves
- Hyperreflexia
- Severe speech impairment
- Developmental delay/intellectual disability

Genetic test

Detection of haploinsufficiency/ pathogenic variant in the ubiquitin protein ligase E3A gene (*UBE3A*)
- 70% due to de novo maternal deletion of 15q11.2-q13
- 2% due to paternal uniparental disomy of 15q11.2-q13
- 2-3% due to imprinting defects
- 25% due to pathogenic variants in maternally derived *UBE3A*

Name: Aniridia - Wilms tumour syndrome

Synonyms:

WAGR (Wilms tumor-aniridia-genitourinary anomalies-intellectual disability syndrome)
Chromosome 11p13 deletion syndrome

ICD 10 – BPA code	*Q131*
ICD 9 – BPA-E*	*74342*
OMIM code	194072; 612469
ORPHA number	ORPHA893

WAGR syndrome is characterized by a complex of congenital abnormalities including aniridia, genitourinary anomalies, and an increased risk of developing Wilms tumor and gonadoblastoma. The syndrome often includes intellectual disability and childhood truncal obesity.

Associated major congenital anomalies

HEAD AND NECK
- Aniridia
- Corneal opacity
- Peters anomaly
- Cataract
- Lens subluxation
- Optic nerve coloboma and hypoplasia
- Microphthalmia

GENITOURINARY
- Hypospadias
- Uterine anomalies
- Ambiguous genitalia

Dysmorphic features/minor anomalies

- Cryptorchidism

Other

- Strabismus
- Glaucoma
- Keratitis
- Hemihyperplasisa
- Obesity
- Nephroblastoma (Wilms tumor)
- Gonadoblastoma
- Variable neurologic abnormalities
- Developmental delay/intellectual disability

Genetic test

Microdeletion of 11p13 minimally involving Wilms tumor 1 gene (*WT1*) and Paired box protein (*PAX 6*)

Name: Apert syndrome

Synonyms:

Acrocephalosyndactyly type1 and type 2
Apert-Crouzon syndrome
Vogt cephalodactyly

ICD 10 – BPA code	Q8701
ICD 9 – BPA-E*	*755500/02*
OMIM code	101200
ORPHA number	ORPHA87

Apert syndrome is characterized by craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet with a tendency of fusion of bony structures.

Associated major congenital anomalies

HEAD AND NECK
- Acrobrachycephaly /turribrachycephaly
- Craniosynostosis (coronal)
- Jugular foraminal stenosis
- Abnormal semicircular canals

CARDIOVASCULAR
- Ventricular septal defect

ABDOMEN
- Esophageal atresia

GENITOURINARY
- Vaginal atresia
- Hydronephrosis

SKELETAL
- Cervical vertebrae fusion, usually at C5 to C6
- Synostosis of radius and humerus
- Fusion of carpal bones
- Symmetric osseous and/or cutaneous syndactyly of hands and feet
- Polydactyly (rare)
- Single nail common to digits 2 to 4

NEUROLOGIC
- Agenesis of the corpus callosum
- Ventriculomegaly/hydrocephalus
- Chiari I malformation

Dysmorphic features/minor anomalies

- Macrocephaly
- Large /late-closing fontanel
- High, broad forehead
- Midface hypoplasia
- Shallow orbits, proptosis, hypertelorism, downslanting palpebral fissures
- Depressed nasal bridge, choanal stenosis or atresia
- High arched /narrow palate, malocclusion
- Mandibular prognathism
- Pyloric stenosis
- Broad distal phalanx of thumb
- Broad distal hallux
- Cryptorchidism
- Ectopic anus
- Absent septum pellucidum
- Posterior fossa arachnoid cyst

Other

- Chronic otitis media, hearing loss
- Glaucoma
- Variable presence of developmental delay/intellectual disability

Genetic test

Detection of the pathogenic variant in the fibroblast growth factor receptor-2 gene (*FGFR2*) (10q26.13)

Name: Bardet Biedl syndrome

Synonyms:
BBS

ICD 10 – BPA code	8781
ICD 9 – BPA-E*	759820
OMIM code	209900
ORPHA number	ORPHA110

Bardet-Biedl syndrome is a ciliopathy characterized by retinitis pigmentosa leading to night blindness and ultimately to visual loss, truncal obesity, kidney dysfunction, postaxial polydactyly, cognitive impairment, behavioural dysfunction, male hypogonadism, renal abnormalities and female genitourinary anomalies. Presence of 4 major (in red) or 3 major and 2 minor features is needed for clinical diagnosis.

Associated major congenital anomalies

HEAD AND NECK
- Cataract (sec)
- Hypodontia

GENITOURINARY
- Hypogenitalism in males
- Various genital anomalies in females (hypoplastic fallopian tubes, uterus, and ovaries, vaginal atresia; duplex uterus; hydrocolpos, hydrometrocolpos; vesico-vaginal fistula etc)
- Renal anomalies - dysplasia, polycystic kineys

SKELETAL
- Polydactyly, usually postaxial
- Brachydactyly
- Syndactyly

Dysmorphic features/minor anomalies

- High arched palate
- Dental crowding
- Cryptorchidism

Other

- Rod-cone dystrophy - onset by end of 2nd decade, retinitis pigmentosa, retinal degeneration, strabismus
- Hepatic fibrosis
- Diabetes mellitus
- Obesity
- Hypogonadotropic hypogonadism in males
- Ataxia
- Hypertonia (especially lower limbs)
- Behavioural abnormalities
- Speech delay/disorder
- Developmental delay/intellectual disability

Genetic test

Detection of the pathogenic variant in at least 19 genes known to be associated with BBS: *BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LZTFL1 (BBS17), BBIP1 (BBS18), and IFT27 (BBS19).*

Name: Beckwith-Wiedemann syndrome

Synonyms:

EMG syndrome

Exomphalos-macroglossia-gigantism syndrome

ICD 10 – BPA code	Q8730
ICD 9 – BPA-E*	759874
OMIM code	130650
ORPHA number	ORPHA116

Beckwith Wiedemann syndrome is a complex overgrowth syndrome characterized by prenatal and postnatal macrosomia, macroglossia, abdominal wall defects, visceromegaly, and an increased risk of developing embryonal tumours, most commonly Wilms tumour and hepatoblastoma. Other distinctive features are neonatal hypoglycemia, grooves/creases in the ear lobes, adrenocortical cytomegaly, renal abnormalities, and hemihyperplasia.

Associated major congenital anomalies

HEAD AND NECK
- Cleft lip/palate

CARDIOVASCULAR
- Cardiomyopathy /cardiomegaly
- Ventricular septal defect
- Atial septal defect

ABDOMEN
- Omphalocele

GENITOURINARY
- Renal medullary dysplasia
- Medullar cystic kidney
- Renal agenesis/hypoplasia
- Megaurether

NEUROLOGIC
- Posterior fossa abnormalities (rare)
- Dandy-Walker malformation (rare)

Dysmorphic features/minor anomalies

- Metopic ridge, large fontanel, prominent occiput
- Coarse facial features, midfacial hypoplasia
- Nevus flammeus or haemangiomas
- Linear ear lobe creases, posterior helical indentations
- Macroglossia
- Diastasis recti
- Umbilical hernia
- Vesicoureteral reflux
- Overgrowth of external genitalia
- Cryptorchidism

Other

- Placental mesenchymal dysplasia
- Generalized overgrowth (macrosomia)
- Neonatal hyperinsulinemic hypoglycemia
- Visceromegaly (hepatomegaly, splenomegaly, pancreas, kidneys)
- Nephrocalcinosis/ nephrolithiasis
- Hemihyperplasia
- Advanced bone age
- Adrenocortical cytomegaly

Genetic test

- Duplication/deletion, translcation/inversion of imprinted region of 11p15.5
- Imprinting defect or UDP of the 11p15.5
- Pathogenic variant in the cyclin-dependent kinase inhibitor 1C gene (*CDKN1C*)
- Pathogenic variant in the nuclear receptor binding SET domain protein 1 (*NSD1*)
- Pathogenic variant in the *KCNQ1*-overlapping transcript 1 gene *(KCNQ1OT1*)

Name: Blepharophimosis-epicanthus inversus-ptosis syndrome

Synonyms:
Blepharophimosis types 1 and 2

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*74360*
OMIM code	110100
ORPHA number	ORPHA126

Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) is characterized by a complex bilateral congenital eyelid malformation including blepharophimosis, ptosis, epicanthus inversus, and telecanthus that can appear associated with (type I) or without premature ovarian failure (type II).

Associated major congenital anomalies

HEAD AND NECK
- Blepharophimosis
- Ptosis
- Microphthalmia
- Microcornea

GENITOURINARY
- Small uterus
- Small ovaries

Dysmorphic features/minor anomalies

- Pronounced arch of eyebrows
- Telecanthus
- Epicanthus inversus
- Lacrimal duct abnormalities
- Simple ears, cup-shaped ears
- Flat, broad nasal bridge
- Short philtrum
- High-arched palate

Other

- Strabismus, hypermetropia, nystagmus
- Characteristic backward head tilt
- Scant pubic and axillary hair (females)
- Amenorrhea, female infertility, menstrual irregularities, premature ovarian failure
- Elevated serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), low estrogen and progesterone

Genetic test

Detection of the pathogenic variant in the forkhead transcription factor *FOXL2* gene (3q22.3)

Name: Branchiootorenal syndrome

Synonyms
BOR syndrome
Melnick Fraser syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*75989*
OMIM code	130650; 610896
ORPHA number	ORPHA107

Branchiootorenal syndrome is characterized by branchial arch anomalies (branchial clefts, fistulae, cysts), sensorineural, conductive, or mixed hearing loss, structural defects of the outer, middle, and inner ear, and renal anomalies (urinary tree malformation, renal hypoplasia or agenesis, renal dysplasia, renal cysts).

Associated major congenital anomalies

HEAD AND NECK
- Cochlear malformation, enlargement of the vestibular aqueduct
- Middle ear malformation
- Cleft palate

GENITOURINARY
- Renal anomalies:
  - Renal collecting system anomalies
  - Renal dysplasia/agensis
  - Polycystic kidneys
  - Abnormal rotation of the kidneys

Dysmorphic features/minor anomalies

- Long, narrow face
- Preauricular pits, microtia, cup-shaped ears, malformed/ hypoplastic pinnae, narrowed external ear canal, , stapes fixation
- Lacrimal duct aplasia or stenosis
- High, arched palate
- Branchial cleft, fistulas, sinuses or cysts
- Vesicoureteral reflux

Other

- Conductive/ sensorineural/mixed hearing impairment
- Facial nerve paralysis

Genetic test

Detection of the pathogenic variant in the eyes absent-1 gene (*EYA1*) (8q13.3) in 50% of cases, chromosomal rearregemnts of 8q13.3 in 20% of cases, rarely pathogenic variants in *SIX1* and *SIX5* gene

Name: CHARGE syndrome

Synonyms:

Coloboma-heart defects-atresia choanae-retardation of growth and development-genital anomalies-ear abnormalities syndrome

Hall-Hittner syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*75989*
OMIM code	214800
ORPHA number	ORPHA138

CHARGE syndrome is a multiple congenital anomaly syndrome characterized by C-coloboma of iris or retina; H-heart defects, A-atresia/stenosis of the choanae, R-retardation of growth and development, G-genital anomalies, E - ear anomalies. Retinal changes and cranial nerve dysfunction and other anomalies are often present as well.

Associated major congenital anomalies

HEAD AND NECK

- Microcephaly
- Colobomas (iris, choroid, retina, disc, and optic nerve)
- Anophthalmia
- Microphthalmia
- Ptosis
- Posterior choanal atresia or stenosis (membranous and/or bony)
- Middle and inner ear anomalies (e.g. Mondini dysplasia)
- Hypoplasia/aplasia of semicircular canals
- Cleft lip/palate
- Micrognathia

CARDIOVASCULAR

- Tetralogy of Fallot
- Atrial septal defect
- Ventricular septal defect
- Double-outlet right ventricle
- Pulmonary valve stenosis
- Patent ductus arteriosus

GASTROINTESTINAL

- Tracheoesophageal fistula/esophageal atresia
- Duodenal atresia
- Anal atresia/ stenosis

GENITOURINARY

- Horseshoe kidney
- Hydronephrosis

SKELETAL

- Ulnar hypoplasia, tibial aplasia (rare)
- Bifid femur (rare

Dysmorphic features/minor anomalies

- Square face, malar flattening, facial asymmetry
- Hypertelorism, downslanting palpebral fissures
- Smal, cup-shaped ears
- Hypoplastic labia
- Cryptorchidism, micropenis
- Short fingers

Other

- Postnatal growth retardation
- Cranial nerve dysfunction resulting in hyposmia or anosmia, unilateral or bilateral facial palsy (40%), impaired hearing, swallowing problems (70%-90%)
- Hypothalamic-hypophyseal dysfunction - growth hormone deficiency, gonadotropin deficiency
- Delayed pubertal development
- Parathyroid hypoplasia, hypothyroidism
- Thymic hypoplasia or aplasia
- Variable degee of developmental delay/intellectual disability
- Autistic spectrum disorders

Genetic test

Detection of the pathogenic variants in the chromodomain helicase DNA-binding protein 7 gene (*CHD7*) (8q12.2)

Name: Clediocranial dysplasia
Synonyms:
Clediocranial dysostosis

ICD 10 – BPA code	Q7402
ICD 9 – BPA-E*	755551
OMIM code	119600; 216330
ORPHA number	ORPHA1452

Cleidocranial dysplasia is characterized by hypoplasia or aplasia of the clavicles and abnormal facility in opposing the shoulders, persistence of wide-open fontanels and skull sutures, multiple dental abnormalities, wide pubic symphysis, short middle phalanx of the fifth fingers and often vertebral anomalies.

Associated major congenital anomalies

HEAD AND NECK
- Cleft palate
- Micrognathia

SKELETAL
- Wormian bones
- Calvarial thickening
- Hypoplastic paranasal sinuses
- Small scapula
- Hypoplastic/aplastic clavicles
- Short ribs
- Scoliosis/ kyphosis
- Broad femoral head with short femoral neck
- Coxa vara
- Hypoplastic iliac wings
- Hand abnormalities
  - Brachydactyly
  - Cone-shaped phalangeal epiphyses
  - Short middle phalanges of second and 5th fingers
  - Pseudoepiphyses of the metacarpal and metatarsal bones

NEUROLOGIC
- Syringomyelia

Dysmorphic features/minor anomalies

- Delayed fontanelle closure/ anterior fontanelle open in adults
- Frontal/ occipital/parietal bossing , metopic groove
- Midface hypoplasia
- Hypertelorism
- Low nasal bridge
- Narrow, high-arched palate
- Dental abnormalities: delayed eruption of teeth, supernumerary teeth, retention cysts, enamel hypoplasia, dental crowding, malocclusion
- Prognathia
- Cervical ribs
- Narrow thorax
- Short thumbs

Other

- Short stature, moderate
- Deafness
- Abnormal facility in opposing the shoulders, sloping shoulders
- Recurrent infections of upper respiratory

Genetic test

Detection of the pathogenic variant in the runt-related transcription factor 2 gene (*RUNX2*) (6p21.1) (60-70% of patients)

Name: Cockayne syndrome
Synonyms:

ICD 10 – BPA code	Q8711
ICD 9 – BPA-E*	759826
OMIM code	133540; 214150; 216400; 216411; 278780; 610756; 610758; 616570
ORPHA number	ORPHA191; 90321; 90322; 90324

The Cockayne syndrome (CS) is presenting with microcephaly, characteristic facial cachectic appearance, cutaneous photosensitivity, progressive growth failure, and developmental delay. Other prominent symptoms include sensorineural hearing loss, pigmentary retinopathy, cataracts, joint contractures, hypertension, atherosclerosis, diabetes, abnormal renal function and progressive neurological decline presenting as combination of pyramidal, extrapyramidal, cerebellar and peripheral symptoms. CS starts usually immediately after birth, but severity and the timing of the presentation vary, forming a continuous spectrum that has led to the differentiation of type I (or classical CS), type II (or early-onset CS), and type III (or mild CS).

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly, progressive
- Cataracts
- Microphthalmos
- Iris hypoplasia
- Microcornea

SKELETAL
- Kyphosis
- Vertebral body abnormalities
- Intervertebral calcifications
- Small, squared pelvis
- Hypoplastic iliac wings
- Joint contractures

Dysmorphic features/minor anomalies

- Loss of facial adipose tissue
- Delayed eruption of deciduous teeth, absent/hypoplastic teeth
- Mandible prognathism
- Micropenis, cryptorchidism

Other

- Severe intrauterine/postnatal growth retardation
- Precociously senile, cachectic appearance,
- Photosensitivity of the skin, scarring, pigmentation, atrophy of skin, dry skin
- Increased cellular sensitivity to UV light
- Sensorineural hearing loss
- Pigmentary retinopathy, optic atrophy, nistagmus, cataract
- Cardiac arrhythmias, hypertension
- Hepatosplenomegaly
- Basal ganglia/ subcortical white matter/ cerebellar calcifications, patchy demyelination of subcortical white matter
- Seizures, ataxia, tremor, weakness, peripheral neuropathy

Genetic test

Detection of pathogenic variants in CSA (*ERCC8*) (5q12.1) or CSB (*ERCC6*) (10q11.23) genes. Approximately 80% of CS patients belong group CSB.

Name: Cornelia de Lange syndrome

Synonyms:

Brachmann-de Lange syndrome
de Lange syndrome
Typus degenerativus Amstelodamensis

ICD 10 – BPA code	8712
ICD 9 – BPA-E*	759821
OMIM code	122470; 300590; 300882; 610759; 614701
ORPHA number	ORPHA199

Cornelia de Lange syndrome (CdLS) is a cohesionopathy, a multiple congenital anomaly/intellectual disability syndrome consisting of characteristic dysmorphic features, microcephaly, hypertrichosis, upper limb defects, growth retardation, developmental delay and a variety of associated anomalies. There is genetic heterogeneity and at present five types are recognized.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Cleft lip/palate

CARDIOVASCULAR
- Congenital heart defect

RESPIRATORY
- Congenital diaphragmatic hernia

GENITOURINARY
- Hypospadias

SKLELETAL
- Limb deficiency/shortening (mainly upper limbs)
- Oligodactyly
- Syndactyly

Dysmorphic features/minor anomalies

- Brachycephaly, low anterior hairline
- Arched eyebrows, synophrys, long curly eyelashes, ptosis
- Low-set posteriorly rotated and/or hirsute ears with thickened helices
- Depressed nasal bridge, short nose, anteverted nostrils
- Thin upper lip, downturned corners of the mouth
- High arched palate
- Small widely-spaced teeth
- Long philtrum
- Micrognathia
- Hypoplastic nipples
- 5th finger clinodactyly
- Small hand and feet
- Cryptorchidism, hypoplastic genitalia

Other

- Prenatal growth retardation/ short stature
- Sensorineural/conductive hearing loss

Genetic test

Detection of the pathogenic variants in the Nipped-B-like (*NIPBL*) (5p13.2) (60%), *SMC1A* (Xp11.22)(5%), *SMC3* (10q25.2) (1-2%), *RAD21* (8q24.11) (<1%) or *HDAC8* (Xq13.1) (4%) genes.

Name: Crouzon syndrome

Synonyms:

Craniofacial dysostosis type I
Crouzon craniofacial dysostosis
Crouzon disease

ICD 10 – BPA code	Q751
ICD 9 – BPA-E*	75601
OMIM code	123500
ORPHA number	ORPHA207

Crouzon syndrome is an autosomal dominant disorder characterized by craniosynostosis causing secondary alterations of the facial bones and facial structure. Common features include brachycephaly, hypertelorism, exophthalmos and external strabismus, parrot-beaked nose, short upper lip, hypoplastic maxilla, and a relative mandibular prognathism.

Associated major congenital anomalies

HEAD AND NECK
- Craniosynostosis (coronal, sagittal, lambdoid sutures)
- Atretic external auditory canals

CARDIOVASCULAR
- Coarctation of aorta
- Patent ductus arteriosus

SKELETAL
- Cervical spine abnormalities

NEUROLOGIC
- Progressive hydrocephalus, often with tonsillar herniation

Dysmorphic features/minor anomalies

- Brachycephaly
- Frontal bossing
- Maxillary hypoplasia
- Shallow orbits, proptosis, external strabismus
- Parrot-beaked nose
- High arched palate, lateral palatal swellings
- Short upper lip, dental crowding
- Mandibular prognathism

Other

- Exposure conjunctivitis/keratitis, external strabismus, optic atrophy
- Sleep apnea
- Sensorineural /conductive hearing loss
- Occasionally developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in the fibroblast growth factor receptor 2 gene (*FGFR2*) (10q26.13)

Name: Dubowitz syndrome
Synonyms:

ICD 10 – BPA code	Q8713
ICD 9 – BPA-E*	*75989*
OMIM code	223370
ORPHA number	ORPHA235

Dubowitz syndrome is a rare multiple congenital syndrome characterized primarly by growth retardation, microcephaly, distinctive facial dysmorphism, cutaneous eczema, mild to severe intellectual deficit and genital abnormalities.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Microphthalmia
- Megalocornea
- Cataract
- Iris hypoplasia
- Iris coloboma

GENITOURINARY
- Hypospadias

Dysmorphic features/minor anomalies

- Sparse hair
- Triangular head, facial asymmetry
- Shallow supraorbital ridge
- High, sloping forehead
- Sparse lateral eyebrows, short palpebral fissures, telecanthus, ptosis
- Prominent, low-set, dysplastic ears
- Broad nasal bridge and nasal tip
- High-arched palate, submucous cleft palate, velopharyngeal insufficiency, delayed eruption, missing teeth
- Micrognathia
- Inguinal hernia
- Sacral dimple
- Cryptorchidism
- Fifth finger clinodactyly
- Syndactyly of toes or fingers (2-3)

Other

- Intrauterine and postnatal growth retardation
- High-pitched or hoarse voice
- Cutaneous eczema
- Recurrent infections
- Malignancies
- Hyperactivity, attention deficit
- Variable developmental delay/intellectual

Genetic test

None

Name: **Ehlers Danlos syndrome**
Synonyms:

ICD 10 – BPA code	Q796
ICD 9 – BPA-E*	75685
OMIM code	130000 + other
ORPHA number	ORPHA287

Ehlers-Danlos syndrome is a large group of connective tissue disorders characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility. Signs vary widely based on which type of EDS the patient has. Very rarely EDS is associated with congenital anomalies. To put the right OMIM or ORPHA code (at present 26 entities) detailed clinical evaluation and genetic testing is needed.

Associated major congenital anomalies

HEAD AND NECK
- Agenesis of multiple teeth (EDS VIII)

CARDIOVASCULAR
- Valvular defects

SKELETAL
- Joint dislocation (hip, shoulder, elbow, knee, or clavicle)
- Scoliosis
- Kyphosis

Dysmorphic features/minor anomalies

- Midface hypoplasia
- Gingival hyperplasia with varying degrees of hyperkeratosis, microdontia
- Umbilical or inguinal hernias

Other

- Joint hypermobility
- Skin hyperextensibility, fragility, abnormal scar formation
- Sensorineural hearing loss (ORPHA300179)
- Myopathy (ORPHA300179)
- Platelet dysfunction (ORPHA75501)
- Osteopenia, fractures (ORPHA230857)
- Short stature

Genetic test

Detection of pathogenic variants in the one of the numerous *EDS* genes

Name: Fragile X syndrome

Synonyms:
FRAXA syndrome
Martin-Bell syndrome

ICD 10 – BPA code	Q992
ICD 9 – BPA-E*	75983
OMIM code	300624
ORPHA number	ORPHA908

Fragile X syndrome is characterized by moderate to severe intellectual disability and distinct behavioural phenotype. The characteristic facial features (long face, large ears, and prominent jaw) and macroorchidism appear progressively during infancy and childhood.

Associated major congenital anomalies

CARDIOVASCULAR
- Mitral valve prolapse
- Aortic root dilatation

SKELETAL
- Pectus excavatum
- Scoliosis

Dysmorphic features/minor anomalies

- Macrocephaly
- Large forehead
- Long face
- Prominent jaw
- Large protruding ears
- Macroorchidism (of later onset)
- Congenital pes planus

- Hyperextensible finger joints

Other

- Hypotonia
- Joint laxity
- Soft and smooth skin
- Periventricular heterotopia
- Seizures
- Hyperactive behavior
- Shyness, gaze aversion
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in *FMR1* (Xq27.3) gene. Most cases (98%) caused by expanded trinucleotide repeat (CGG)n

Name: Fraser syndrome

Synonyms:

Cryptophthalmos-syndactyly
Ullrich-Feichtiger's syndrome

ICD 10 – BPA code	Q8702
ICD 9 – BPA-E*	*759892*
OMIM code	219000
ORPHA number	ORPHA2052

Fraser syndrome is characterized by variable expression of cryptophthalmos, cutaneous syndactyly, laryngeal and urogenital anomalies. Various other anomalies including craniofacial, anorectal, skeletal, and heart defects may be also present.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Cryptophthalmos
- Microphthalmos/anophthalmos
- Cataract
- Coloboma of iris
- Coloboma of eyelid
- Middle ear anomalies
- External ear anomalies
- Midline nasal cleavage
- Cleft lip/ palate

RESPIRATORY
- Laryngeal atresia/stenosis

GASTROINTESTINAL
- Tracheoesophageal fistula/esophageal atresia
- Duodenal atresia
- Agenesis/atresia/stenosis of anus

GENITOURINARY
- Abnormal genitalia
  - Hypospadias
  - Vaginal atresia
  - Bicornuate uterus
  - Ambiguous genitalia
- Renal agenesis/hypoplasia
- Atresia /hypoplasia of bladder

SKELETAL
- Syndactyly

NEUROLOGIC
- Meningomyelocele
- Encephalocele

Dysmorphic features/minor anomalies

- Hypertelorism
- Hypoplastic, notched nares, broad, low nasal bridge
- Teeth crowding
- Widely spaced nipples
- Umbilical anomaly
- Small penis
- Clitoral enlargement
- Cryptorchidism

Other

- Blindness
- Conductive hearing loss
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in the *FRAS1* (4q21.21) gene (*FRAS1*) or in the *FRAS1*-related extracellular matrix protein 2 gene (*FREM2*) (13q.3) or *GRIP1*(12q14.3)

Name: Frontonasal dysplasia

Synonyms:

Frontorhiny
ALX3-related frontonasal dysplasia
Isolated median cleft face syndrome

ICD 10 – BPA code	Q7581
ICD 9 – BPA-E*	*75400*
OMIM code	136760
ORPHA number	ORPHA391474

Frontonasal dysplasia or median cleft syndrome is defined as 2 or more of the following: (1) hypertelorism; (2) broadening of the nasal root; (3) median facial cleft affecting the nose and/or upper lip and palate; (4) unilateral or bilateral clefting of the alae nasi; (5) lack of formation of the nasal tip; (6) anterior cranium bifidum occultum and (7) a V-shaped or widow's peak frontal hairline.
Note that frontonasal dysplasia may be syndromic, occurring in association with other anomalies, such as alopecia and genital anomalies (ORPHA228390, ALX4-related FNDAG), or variable central nervous system anomalies and limb defects (tibial hypoplasia/aplasia, club foot, symmetric preaxial polydactyly of the feet and bilateral clubbed and thickened nails of halluces

Associated major congenital anomalies

HEAD AND NECK
- Cranium bifidum occultum
- Frontal cutaneous lipoma
- Microphthalmia
- Ptosis
- Coloboma
- Cataract
- Vertical midline cleft of the nose and/or upper lip/palate, cleft of the wings of the nose

CARDIOVASCULAR
- Tetralogy of Fallot

THORAX
- Pectoral muscle hypoplasia/aplasia (Poland syndrome)

SKELETAL
- Brachydactyly, camptodactyly
- Clinodactyly

NEUROLOGIC
- Lipoma of corpus callosum

Dysmorphic features/minor anomalies

- Widow's peak
- Maxillary hypoplasia
- Hypertelorism, telecanthus, epicanthal folds
- Preauricular tags, low-set ear
- Broad nasal root, variable bifid nose, broad notched nasal tip, nasal tag, notched alae nasi

Other

- Conductive hearing loss
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in the aristaless-like homeobox 3 gene (*ALX3*) (1p13.3)

Name: Gorlin-Chaudhry-Moss syndrome

Synonyms:

Craniofacial dysostosis-genital, dental, cardiac anomalies syndrome
Cranofacial dysostosis-hypertrichosis-hypoplasia of labia majora syndrome
Dental and eye anomalies-patent ductus arteriosus-normal intelligence syndrome
GCM syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*759898*
OMIM code	233500
ORPHA number	ORPHA2095

Gorlin-Chaudhry-Moss syndrome is characterized by craniofacial dysostosis, facial dysmorphism, conductive hearing loss, generalised hypertrichosis, dental anomalies, hypoplastic distal phalanges, umbilical hernia, and genital hypoplasia.

Associated major congenital anomalies

HEAD AND NECK

- Craniosynostosis (coronal)
- Microphthalmia
- Upper eyelid colobomas
- Hypoplastic maxillary bones
- Hypoplastic nasal bones
- Ptosis
- Hypodontia

CARDIOVASCULAR

- Patent ductus arteriosus

SKELETAL

- Hypoplastic distal phalanges, small/aplastic nails,
- Syndactyly (cutaneous)

Dysmorphic features/minor anomalies

- Brachycephaly
- Low anterior and posterior hairline
- Depressed supraorbital ridge
- Midface hypoplasia
- Lateral flaring of eyebrows, synophrys, hypertelorism, downslanting, small palpebral fissures, ectropion of lower eyelid
- Bifid nasal tip, prominent columella
- High-arched, narrow palate, hypo/microdontia, abnormally shaped teeth
- Umbilical hernia
- Hypoplastic labia majora
- Hypoplastic distal phalanges
- Smal/aplastic nails (in some patients)

Other

- Short stature
- Stocky body build
- Conductive hearing loss
- Hypertrichosis (scalp, arms, legs, back)

Genetic test

None

Name: Hallermann-Streiff syndrome

Synonyms:

Oculomandibulofacial syndrome
Oculomandibular dysostosis
François dyscephalic syndrome

ICD 10 – BPA code	Q8705
ICD 9 – BPA-E*	756050
OMIM code	234100
ORPHA number	ORPHA2108

Hallermann-Streiff syndrome is characterized by a brachycephaly with frontal bossing, hypotrichosis, bird-like facies (beak-shaped nose and retrognathia), microphthalmia, cataracts, skin atrophy, dental anomalies, and proportionate short stature.

Associated major congenital anomalies

HEAD AND NECK

- Microcephaly
- Microphthalmia
- Ptosis
- Cataracts
- Iris coloboma
- Choroid coloboma
- Optic disc coloboma
- Hypodontia/supernumerary teeth

SKELETAL

- Thin calvarium
- Wormian bones
- Scoliosis
- Spina bifida
- Thin, gracile ribs, long bones and metacarpals

Dysmorphic features/minor anomalies

- Thin hair, hypotrichosis, alopecia
- Brachycephaly
- Frontal/ parietal bossing
- Malar hypoplasia
- Sparse eyebrows and eyelashes, downward slanting palpebral fissures, blue sclerae
- Thin, small pointed or beak-shaped nose, nasal cartilage hypoplasia
- Microstomia, thin lips, everted lower lip, high arched, narrow palate, neonatal teeth, enamel hypoplasia
- Micrognathia, retrognathia
- Tracheomalacia
- Cryptorchidism

Other

- Low birth weight, proportionate small stature
- Skin atrophy (face and scalp suttural areas), telangiectases, xerosis
- Hyperextensible joints
- Nystagmus, strabismus
- Obstructive sleep apnea
- Osteoporosis
- Variable intellectual disability

Genetic test

None

Name: Holt-Oram syndrome

Synonyms:

Heart-hand syndrome type 1

Atriodigital dysplasia type

ICD 10 – BPA code	Q8720
ICD 9 – BPA-E*	759842
OMIM code	142900
ORPHA number	ORPHA392

Holt-Oram syndrome is a characterised by high penetrance and variable expression of upper limb abnormalities (always including the radial ray), congenital heart defects and/or conduction abnormalities.

Associated major congenital anomalies

CARDIOVASCULAR

- Atrial septal defect (ostium secundum type)
- Ventricular septal defect
- Atrioventricular septal defect
- Hypoplastic left heart syndrome
- Pulmonary atresia/stenosis
- Patent ductus arteriosus

SKELETAL

Thorax

- Clavicles, abnormalities
- Absent pectoralis major muscle
- Pectus excavatum or carinatum
- Rib anomalies

Spine

- Vertebral anomalies
- Thoracic scoliosis

Limbs

Upper extremities defects:

- Phocomelia of upper extremities
- Hand and/or fingers aplasia/hypoplasia
- Radius agenesis/ hypoplasia
- Ulnar hypoplasia/aplasia
- Humerus hypoplasia/aplasia
- Synostosis of radius and ulna
- Carpal bone anomalies
- Absent thumb
- Bifid thumb
- Triphalangeal thumb
- Syndactyly

Dysmorphic features/minor anomalies

Other

- Conduction abnormalities (paroxysmal atrial fibrillation, sometimes associated with various degrees of atrioventricular block)

Genetic test

Detection of pathogenic variant in the T-Box 5 gene (*TBX5*) (12q24.21)

Name: Hypoglossia-hypodactyly syndrome

Synonyms:

Aglossia-Adactylia
Peromelia with micrognathism
Oromandibular limb hypoplasia
Hanhart syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*759846*
OMIM code	103300
ORPHA number	ORPHA989

Hypoglossia-hypodactyia syndrome is characterized by a hypoplastic mandible, absence of the lower incisors, hypoglossia, and a variable degree of absence of the digits and limbs.

Associated major congenital anomalies

HEAD AND NECK
- Hypoglossia /aglossia
- Clefting or aberrant attachments of tongue
- Cleft lip/palate
- Absence of lower incisors
- Micrognathia

ABDOMINAL
- Gastroschisis
- Splenogonadal fusion

GENITOURINARY
- Unilateral renal agenesis

SKELETAL
- Limb hypoplasia (hands/feet)
- Adactyly/ Hypodactyly (hands/feet)
- Ectrodactyly (hands/feet)
- Club foot

Dysmorphic features/minor anomalies

- Facial asymmetry
- Epicanthus, telecanthus, lower eyelid defects
- Broad nose
- Microstomia
- Retrognathia
- Cryptorchidism

Other

- Cranial nerve palsies (including Möebius sequence)

Genetic test

None

Name: Incontinentia pigmenti
Synonyms:
Bloch-Siemens syndrome
Bloch-Sulzberger syndrome

ICD 10 – BPA code	Q823
ICD 9 – BPA-E*	75735
OMIM code	308300
ORPHA number	ORPHA464

Incontinentia pigmenti is ectodermal dysplasia, usually lethal in males, presenting neonatally in females with highly variable abnormalities of the skin, hair, nails, teeth, eyes, and central nervous system. The skin changes evolve in 4 stages: blistering (from birth to about four months of age) appears along Blashko's lines, evolving to verrucous rash (for several months), swirling macular hyperpigmentation (from about six months of age into adulthood), followed by linear hypopigmentation.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Microphthalmos
- Cataract
- Hypodontia
- Breast aplasia/ hypoplasia

SKELETAL
- Hemivertebrae
- Kyphoscoliosis
- Spina bifida
- Acheiria

NEUROLOGIC
- Cortical atrophy

Dysmorphic features/minor anomalies

- Delayed eruption, conical form, accessory cusps of teeth
- Supernumerary nipple, nipple aplasia/hypoplasia
- Extra ribs

Other
- Alopecia, coarse or thin, sparse hair
- Skin erythema, vesicles, pustules, linear distribution (Stage 1), skin papules, verrucous lesions, hyperkeratosis, affects distal limb and scalp (Stage 2), hyperpigmentation that follows Blaschko's lines and primarily affects trunk (Stage 3), skin pallor, atrophy, and scarring most evident on lower legs (Stage 4)
- Strabismus, uveitis, keratitis, optic atrophy, retinal vascular proliferation, ischemia/ bleeding/ fibrosis/ detachment
- Nail dystrophy
- Seizures
- Intellectual disability

Genetic test

Detection of pathogenic variant in the NF-kappa-B essential modulator gene (*IKBKG*) (Xq28)

Name: Ivemark syndrome

Synonyms:

Right atrial isomerism
Right isomerism sequence
Asplenia with cardiovascular anomalies
Bilateral right-sidedness sequence

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*75989*
OMIM code	208530
ORPHA number	ORPHA97548

Ivemark syndrome is a heterotaxy syndrome including right atrial isomerism (RAI) and left atrial isomerism (LAI). RAI is characterized by complex congenital heart defect, usually complete atrioventricular septal defect with a common atrium and univentricular AV connection, total anomalous pulmonary drainage, and transposition or malposition of the great arteries. Other associated abnormalities include asplenia, bilateral trilobed lungs, midline liver, and as well as *situs inversus* affecting other organs. LAI is characterized by bilateral superior vena cava, interruption of the intrahepatic portion of the inferior vena cava, partial anomalous pulmonary venous drainage, and ventricular septal defect. Patients with LAI may have polysplenia and bilateral bilobed lungs, as well as *situs inversus* affecting other organs.

Associated major congenital anomalies

CARDIOVASCULAR

- Right atrial isomerism
- Dextrocardia
- Common atrium
- Anomalous pulmonary venous return
- Univentricular atrial-ventricular connection
- Atrioventricular septal defect
- Double outlet right ventricle
- Single ventricle with right ventricular morphology
- Complex heart malformation
- Transposition of the great vesells
- Pulmonary outflow tract obstruction
- Pulmonary atresia/stenosis

RESPIRATORY

- Trilobulated/bilobed lungs bilaterally

ABDOMEN

- *Situs inversus*/ambiguous
- Asplenia
- Polysplenia

Dysmorphic features/minor anomalies

Other

Genetic test

Detection of pathogenic variant in the growth/differentiation factor 1 gene (*GDF1*) (19p13.11)

Name: Kartagener syndrome

Synonyms:

Primary ciliary dyskinesia
Dextrocardia-bronchiectasis-sinusitis syndrome
Immotile cilia syndrome, Kartagener type
Siewert syndrome

ICD 10 – BPA code	Q8934
ICD 9 – BPA-E*	759340
OMIM code	244400
ORPHA number	ORPHA98861

Kartagener syndrome is characterized by the combination of primary ciliary dyskinesia and *situs inversus*.

Associated major congenital anomalies

CARDIOVASCULAR
- Dextrocardia

ABDOMEN
- *Situs inversus*
- Asplenia

NEUROLOGIC
- Communicating hydrocephalus

Dysmorphic features/minor anomalies

Other

- Immotile cilia
- Corneal abnormalities
- Conductive deafness, chronic otitis media
- Poorly aerated mastoids, absence of frontal sinuses, chronic sinusitis, nasal polyps, anosmia
- Chronic recurrent respiratory infections
- Bronchiectasis
- Infertility

Genetic test

Detection of pathogenic variants in the dynein, axonemal, intermediate chain 1 gene (*DNAI1*) (9p13.3)

Name: McKusick-Kaufman syndrome

Synonyms:

Hydrometrocolpos-postaxial polydactyly syndrome and congenital heart malformation

McKusick-Kaufman syndrome

Hydrometrocolpos syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*75248*
OMIM code	236700
ORPHA number	ORPHA2473

McKusick-Kaufman syndrome (MKS) is characterized by the combination of postaxial polydactyly, congenital heart disease, and hydrometrocolpos in females and genital anomalies (most commonly hypospadias, cryptorchidism, and chordee) in males. Difficult to differentiate from Bardet Biedel syndrome in early infancy and childhood.

Associated major congenital anomalies

CARDIOVASCULAR

- Congenital heart disease
  - Atrial septal defect
  - Ventricular septal defect
  - AV canal
  - Hypoplastic left ventricle
  - Tetralogy of Fallot
  - Patent ductus arteriosus

ABDOMEN

- Hirschsprung disease
- Imperforate anus
- Rectovaginal fistula

GENITOURINARY

- Hydrometrocolpos
- Transverse vaginal membrane
- Vaginal atresia/stenosis
- Rectovaginal fistula
- Vesicovaginal fistula
- Polycystic kidney

SKELETAL

- Congenital dislocation of the hip
- Postaxial polydactyly
- Syndactyly

Dysmorphic features/minor anomalies

- Cryptorchidism

Other

Genetic test

Detection of pathogenic variants in the *MKKS* gene (20p12.2)

*Because of overlap with Bardet-Biedl syndrome, patients should be followed by ophthalmology for development of cone-rod dystrophy until at least 10 years of age

Name: Klippel-Feil syndrome

Synonyms:
Congenital cervical vertebral fusion
Congenital fused cervical segments

ICD 10 – BPA code	Q761
ICD 9 – BPA-E*	756110
OMIM code	118100; 214300; 613702
ORPHA number	ORPHA2345

Klippel-Feil syndrome is characterised by a defect in the formation or segmentation of the cervical vertebrae resulting in congenitally fused cervical vertebrae. The clinical triad consists of short neck, low posterior hairline, and limited neck movement.

Associated major congenital anomalies

HEAD AND NECK
- Hearing loss, sensorineural
- Hearing loss, conductive
- Cleft palate
- Oligo- and hypodontia

CARDIOVASCULAR
- Ventricuar septal defect

SKELETAL
- Fusion of cervical vertebrae, most often C2-3
- Sprengel anomaly
- Scoliosis
- Spina bifida

Dysmorphic features/minor anomalies

- Short neck
- Low posterior hairline
- Late dentition, high-risk of caries,

Other

- Limited neck range of motion
- Short stature
- Duane anomaly

Genetic test

Detection of pathogenic variants in the growth/differentiation factor 6 gene (*GDF6*) (12p13.31) (AD form) and rarely in the mesenchyme homeobox 1 gene (*MEOX1*) (17q21.31) (AR form)

Name: : Klippel-Trénaunay-Weber syndrome

Synonyms:

Angioosteohypertrophic syndrome

ICD 10 – BPA code	Q8721
ICD 9 – BPA-E*	759840
OMIM code	149000; 608355
ORPHA number	ORPHA2346

Klippel-Trénaunay-Weber syndrome is characterized by blood and lymph vessels dysplasia in a limb, with hypertrophy of the related bones and soft tissues.

Associated major congenital anomalies

CARDIOVASCULAR

- Cutaneous hemangiomata, capillary and cavernous
- Arteriovenous fistula
- Lymphangioma, dysplastic lymphatic system
- Vein anomalies

SKELETAL

- Asymmetric limb growth
- Macrodactyly
- Syndactyly
- Polydactyly
- Oligodactyly

Dysmorphic features/minor anomalies

- Nevus flammeus (port-wine nevus)

Other

- Glaucoma
- Soft-tissue hyperplasia
- Lymphedema
- Cellulitis

Genetic test

None

Name: : Larsen syndrome
Synonyms:

ICD 10 – BPA code	Q7484
ICD 9 – BPA-E*	75581
OMIM code	150250; 245600
ORPHA number	ORPHA503; 284139

Larsen syndrome is skeletal dysplasia characterized by large-joint dislocations (hip, knee and elbow joints, equinovarus) and characteristic craniofacial abnormalities (hypertelorism, prominent forehead, depressed nasal bridge, flattened midface).

Associated major congenital anomalies

HEAD AND NECK
- Anomalies of the auditory ossicles
- Anterior corneal lens opacities
- Cleft lip/palate
- Hypodontia

CARDIOVASCULAR
- Aortic dilatation
- Atrial septal defect
- Ventricular septal defect

RESPIRATORY
- Tracheal stenosis

SKELETAL
Spine
- Cervical vertebrae hypoplasia
- Subluxation or fusion of the cervical vertebrae
- Cervical kyphosis
- Scoliosis
- Wedged vertebrae
- Dislocation of the hip

Limbs
- Dislocations of the elbows
- Dislocations of the wrists
- Dislocations of the knees
- Short metacarpals and metatarsals
- Supernumerary carpal and tarsal bones
- Talipes equinovarus

Dysmorphic features/minor anomalies

- Flat face
- Prominent forehead
- Hypertelorism, shallow orbits
- Depressed nasal bridge
- Tracheomalacia
- Bronchomalacia
- Spatulate thumbs
- Short nails
- Spina bifida occulta
- Cryptorchidism

Other

- Prenatal growth deficiency
- Short stature
- Joint laxity
- Hearing loss, conductive
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variant in the filamin B gene (*FLNB*) (3p14.3)

Name: Laurence-Moon syndrome
Synonyms:

ICD 10 – BPA code	Q8781
ICD 9 – BPA-E*	759822
OMIM code	245800
ORPHA number	ORPHA2377

Laurence-Moon syndrome is characterized by pituitary dysfunction, cerebellar ataxia, peripheral neuropathy, spastic paraplegia, and chorioretinal dystrophy.

Associated major congenital anomalies

HEAD AND NECK
- Cataract

SKELETAL
- Polydacytyly

Dysmorphic features/minor anomalies

- Hypoplastic scrotum
- Micropenis

Other

- Short stature
- Nystagmus, choroidal atrophy, pigmentary retinopathy
- Hypopituitarism
- Obesity
- Ataxia cerebellar
- Peripheral neuropathy
- Renal insufficiency
- Spastic paraplegia
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in the patatin-like phospholipase domain-containing protein 6 gene *PNPLA6* (19p13.2)

Name: Lenz microphthalmia syndrome

Synonyms:

Microphthalmia, Lenz type
Lenz dysplasia
Micropthalmia, syndromic 1

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*74310*
OMIM code	309800
ORPHA number	ORPHA568

Lenz microphthalmia syndrome is characterized by unilateral or bilateral microphthalmia or anophthalmia with or without coloboma in addition to a range of extraocular manifestations such as microcephaly, anomalies of the ears, teeth, fingers, skeleton, genitourinary system and mild to severe intellectual disability. It is allelic to two disorders: oculofaciocardiodental syndrome and premature aging appearance-developmental delay-cardiac arrhythmia syndrome.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Microphthalmia /Anophthalmia
- Microcornea
- Ptosis
- Cataract
- Colobomas of optic disk, choroid, ciliary body, and iris
- Hypodontia

ABDOMEN
- Megacolon

GENITOURINARY
- Hypospadias
- Renal hypoplasia/aplasia
- Hydroureter

SKELETAL
- Underdeveloped clavicle
- Pectus excavatum
- Scoliosis
- Digital anomalies (44%)
  - Double thumbs (in some patients)
  - Syndactyly
  - Clinodactyly
  - Camptodactyly

Dysmorphic features/minor anomalies

- Webbed neck
- Low-set, anteverted, posteriorly rotated, simple, cup shaped, or abnormally modeled ears
- High arched palate
- Irregularly shaped, or widely spaced teeth (50%)
- Laryngotracheobronchomalacia
- Fetal pads of digits
- Cryptorchidism

Other

- Growth retardation
- Blindness, glaucoma
- Hearing loss
- Delayed motor development
- Hypotonia
- Seizures
- Aggressiveness
- Self-mutilation
- Developmental delay/intellectual disability (60%)
- Autistic spectrum

Genetic test

Detection of pathogenic variant in the NatA catalytic subunit of N-alpha-acetyltransferase-10 gene *NAA10* (Xq28)

Name: Marfan syndrome
Synonyms:

ICD 10 – BPA code	Q874
ICD 9 – BPA-E*	759860
OMIM code	154700; 610168
ORPHA number	ORPHA558

Marfan syndrome is a systemic connective tissue disorder involving the ocular, cardiovascular, respiratory and musculo-skeletal system. The diagnosis is based on revised Ghent criteria (Loeys BL et al., J Med Genet 2010).

Associated major congenital anomalies

HEAD AND NECK
- Lens subluxation
- Cataracts

CARDIOVASCULAR
- Mitral valve prolapse/insufficiency
- Tricuspid valve prolapse
- Aortic root dilatation/ aneurysm/ dissection
- Aneurysm of other aortic segments
- Pulmonary artery dilatation

SKELETAL
- Pectus excavatum
- Pectus carinatum
- Scoliosis
- Kyphoscoliosis
- Long bone overgrowth

Dysmorphic features/minor anomalies

- Dolichocephaly
- Long, narrow face
- Malar hypoplasia
- Downslanting palpebral fissures
- High-arched, narrow palate, crowded teeth
- Micrognathia
- Retrognathia
- Inguinal hernia
- Arachnodactyly
- Genu recurvatum

Other

- Disproportionate tall stature, upper to lower segment ratio less than 0.85 Arm span to height > 1.05 (dolichostenomelia)
- Retinal detachment, glaucoma, myopia, strabismus
- Pneumothorax
- Acetabular protrusion
- Striae, decreased subcutaneous fat
- Joint hypermobility
- Decreased muscle mass
- Spondylolisthesis
- Lumbosacral dural ectasia

Genetic test

Detection of pathogenic variants in the fibrillin 1 gene (*FBN1*) (15q21) or in *TGFBR2* gene (chr.3)

Name: McCune-Albright syndrome

Synonyms:

Polyostotic fibrous dysplasia
Gonadotropin-independent female-limited sexual precocity

ICD 10 – BPA code	Q781
ICD 9 – BPA-E*	756512
OMIM code	174800
ORPHA number	ORPHA562

McCune-Albright syndrome is caused by early embryonic postzygotic somatic activating pathogenic variant of *GNAS* present in the mosaic state and characterized by involvement of the skin, skeleton, and the endocrine system. The diagnosis is based on the finding of two or more typical clinical features.

Associated major congenital anomalies

HEAD AND NECK
- Craniofacial hyperostosis

SKELETAL
- Polyostotic fibrous dysplasia
- Progressive scoliosis

Dysmorphic features/minor anomalies

- Large café au lait spots

Other

- Hemihiperplasia
- Deafness
- Blindness
- Hyperfunctioning endocrine disease
  - Hyperthyroidism
  - Hyperparathyroidism
  - Cushing syndrome
  - Precocious puberty
  - Acromegaly
  - Hyperprolactinemia
- Pituitary adenoma
- Gastrointestinal polyps
- Pathologic fractures, bone pain
- Hypophosphatemia

Genetic test

Detection of somatic pathogenic variant in the guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1 gene *GNAS1* (20q13.32)

Name: Meckel Gruber syndrome
Synonyms:
Meckel syndrome
Dysencephalia splanchnocystica

ICD 10 – BPA code	Q6190
ICD 9 – BPA-E*	*75989*
OMIM code	249000+several
ORPHA number	ORPHA564

Meckel-Gruber syndrome is a genetically heterogeneous severe lethal ciliopathy. The minimal diagnostic criteria are most often formulated as the presence of at least 2 of the 3 main manifestations, i.e. bilateral renal cystic dysplasia, occipital encephalocele or other anomalies of the central nervous system, and polydactyly. Additional anomalies such as microphthalmia, facial clefting, heart defects, fibrotic changes in the portal area of the liver, incomplete/ambiguous development of external or internal genitalia are often present.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Microphthalmia/anophthalmia, iris coloboma
- Cleft lip/palate

CARDIOVASCULAR
- Ventricular septal defect, atrial septal defect
- Coarctation of aorta
- Patent ductus arteriosus

RESPIRATORY
- Cleft epiglottis

ABDOMEN
- Asplenia, accessory spleen
- Omphalocele
- Anal stenosis/atresia

GENITOURINARY
- Ambiguous genitalia
- Uterus duplex, unicornuate uterus, uterus bifidum
- Cistic kidney disease
- Renal agenesis, renal hypoplasia/dysplasia
- Accessory kidney, ren arcuatus
- Duplicated ureters

SKELETAL
- Cervical rachishisis
- Short limbs
- Postaxial polydactyly hand/feet

NEUROLOGIC
- Arnold-Chiari malformation
- Encephalocele
- Hydrocephalus
- Dandy-Walker malformation
- Agenesis/hypoplasia of cerebellum
- Olfactory lobe absence
- Agenesis/hypoplasia of corpus callosum

Dysmorphic features/minor anomalies

- Sloping forehead
- Potter-like facies
- Low-set ears
- Hypotelorism/hypertelorism
- Macrostomia
- Natal teeth
- Micrognathia
- Short/ webbed neck
- Single umbilical artery
- Cryptorchidism
- Clinodactyly of the 5th finger
- Bowed long bones

Other

- Fibrotic and/or cystic liver/ductal plate malformation
- Splenomegaly
- Adrenal hypoplasia

Genetic test

Detection of pathogenic variants in at least 12 genes known to cause this autosomal recessive disorder: *MKS1*, *TMEM216 (MKS2)*, *TMEM67(MKS3)*, *CEP290 (MKS4)*, *RPGRIP1L (MKS5)*, *CC2D2A (MKS6)*, *NPHP3 (MKS7)*, *TCTN2 (MKS8)*, *B9D1 (MKS9)*, *B9D2 (MKS10)*, *TMEM231 (MKS11)*, *KIF14 (MKS12)*

Name: Melnick-Needles syndrome
Synonyms:
Melnick-Needles osteodysplasty

ICD 10 – BPA code	*Q778*
ICD 9 – BPA-E*	759845
OMIM code	309350
ORPHA number	ORPHA2484

Melnick-Needles syndrome belongs to the otopalatodigital syndrome spectrum disorder and is associated with short stature, facial dysmorphism, osseus abnormalities involving the majority of the axial and appendicular skeleton resulting in impaired speech and masticatory problems.

Associated major congenital anomalies

HEAD AND NECK
- Delayed cranial suture closure
- Micrognathia

SKELETAL
- Ribbon-like ribs
- Short clavicles
- Mild distal phalangeal hypoplasia
- Cone-shaped epiphyses
- Pelvic hypoplasia
- Coxa valga

GENITOURINARY
- Hydronephrosis

Dysmorphic features/minor anomalies

- Facial asymmetry
- Prominent brow ridge
- Frontal hirsutism
- Hypertelorism
- Exophtalmos
- Full cheeks
- Dental maloclusion
- Relatively small thorax
- Bowing of humerus, radius, ulna, and tibia

Other

- Short stature
- Conductive/sensorineural hearing loss
- Pulmonary hypertension
- Osteoarthritis of the back or hip

Genetic test

Detection of pathogenic variant in the filamin A gene (*FLNA*) (Xq28)

Name: Miller-Dieker syndrome
Synonyms:
Lissencephaly due to 17p13.3 deletion
Monosomy 17p13.3
Telomeric deletion 17p

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*74228*
OMIM code	247200
ORPHA number	ORPHA531

Miller-Dieker syndrome is a contiguous gene deletion syndrome of chromosome 17p13.3, characterised by severe lissencephaly (type 1), distinct facial features, developmental and neurologic abnormalities. Additional congenital anomalies include omphalocele and congenital heart defects.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Cataract
- Cleft palate
- Micrognathia

CARDIOVASCULAR
- Tetralogy of Fallot
- Ventricular septal defect
- Valvular pulmonic stenosis

ABDOMEN
- Duodenal atresia
- Omphalocele

GENITOURINARY
- Cystic kidney
- Pelvic kidney

SKELETAL
- Polydactyly
- Camptodactyly
- Clinodactyly

NEUROLOGIC
- Lysencephaly type I
- Agyria, pachygyria, heterotopia
- Absent/hypoplastic corpus callosum

Dysmorphic features/minor anomalies

- Bitemporal narrowing
- Vertical soft tissue ridging on forehead
- Furrowing of forehead
- Upslanting palpebral fissures
- Low-set, posteriorly rotated ears
- Midface hypoplasia
- Small nose, anteverted nares
- Prominent upper lip with thin vermilion border
- Inguinal hernia
- Cryptorchidism

Other

- Polyhydramnios
- Intrauterine growth retardation
- Feeding problems
- Hypotonia/motor delay
- Progressive spastic paraplegia
- Infantile spasms, epilepsy
- Developmental delay/intellectual disability

Genetic test

Detection of microdeletion of 17p13.3. involving the lissencephaly 1 gene (*LIS1*) and the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon isoform gene (*YWHAE*)

Name: Noonan syndrome
Synonyms:
Male Turner syndrome
Female pseudo-Turner syndrome
Turner phenotype with normal karyotype

ICD 10 – BPA code	Q8714
ICD 9 – BPA-E*	759896
OMIM code	163950 + several
ORPHA number	ORPHA648

Noonan syndrome is characterized by short stature, typical facial dysmorphism, congenital heart defects, learning problems, pectus excavatum, impaired blood clotting, and a characteristic dysmorphicl features

Associated major congenital anomalies

HEAD AND NECK
- Ptosis

CARDIOVASCULAR
- Atrial/ventricular septal defects
- Pulmonary valve stenosis
- Coarctation of the aorta
- Hypertrophic cardiomyopathy

SKELETAL
- Pectus carinatum and inferior
- Pectus excavatum
- Kyphosis/Scoliosis

Dysmorphic features/minor anomalies

- Curly hair, sparse eyebrows,
- Downslanting palpebral fissures, hypertelorism
- Low set posteriorly rotated ears, thickened helix
- Short/webbed neck
- Cryptorchidism

Other

- Short stature
- Failure to thrive
- Defects in coagulation and platelet systems
- Lymphatic dysplasia
- Developmental delay/ intellectual disability

Genetic test

Detection of pathogenic variants in *PTPN11* (12q24.13) in 50% of affected individuals, *SOS1* (2p22.1)in approximately 13%, RAF1 (3p25.2) and *RIT1* (1q22) each in 5%, and *KRAS* (12p12.1) in fewer than 5%. Other genes in which pathogenic variants have been reported to cause Noonan syndrome in fewer than 1% of cases include *NRAS* (1p13.2), *BRAF* (7q34), and *LZTR1*(22q11.21).

Name: Orofaciodigital syndrome type 1

Synonyms:
OFD1
Papillon-Léage-Psaume syndrome

ICD 10 – BPA code	Q8707
ICD 9 – BPA-E*	759802
OMIM code	311200
ORPHA number	ORPHA2750

Orofaciodigital syndrome type I (OFD1) is X-linked dominant ciliopathy that predominantly affects females as it is lethal in males. It is characterized by anomalies of the face, oral cavity, and digits. The central nervous system and kidneys are often involved as well.

Associated major congenital anomalies

HEAD AND NECK
- Multiple and/or hyperplastic frenuli between the buccal mucous membrane and alveolar ridge
- Lobated/bifid tongue
- Median cleft lip
- Cleft palate

SKELETAL
- Syndactyly
- Brachydactyly of hands
- Preaxial polydactyly of feet
- Duplicated hallux, great toe

GENITOURINARY
- Polycistic kidney disease (adult)

NEUROLOGIC
- Agenesis of corpus callosum
- Intracerebral cyst
- Cerebellar/vermis hypoplasia
- Focal polymicrogyria
- Heterotopia
- Dandy-Walker malformation

Dysmorphic features/minor anomalies

- Sparse hair
- Telecanthus
- Hypoplasia of the alae nasi
- Hypodontia, and other dental anomalies
- Micrognathia
- Asymmetric shortening of digits
- Clinodactily of the 5th finger

Other

- Intellectual disability
- Fibrocystic disease of liver and pancreas in adulthood

Genetic test

Detection of pathogenic variant in *OFD1* protein gene (Xp22.2)

Name: Orofacialdigital syndrome type 2

Synonyms:

Mohr syndrome

OFD2

ICD 10 – BPA code	Q8707
ICD 9 – BPA-E*	759802
OMIM code	252100
ORPHA number	ORPHA2751

Orofacialdigital syndrome type 2 is characterized by hand and feet deformities, facial deformities, midline cleft of the upper lip and tongue hamartomas.

Associated major congenital anomalies

HEAD AND NECK

- Microcephaly
- Midline cleft of the upper lip
- Tongue lobulated with multiple and hypertrophied frenula
- Absence of medial incisors

SKELETAL

- Wormian cranial bones
- Pectus excavatum
- Scoliosis
- Brachydactyly
- Syndactyly
- Postaxial polydactyly of hands and feet
- Partial duplication of hallux

GENITOURINARY

- Hydronephrosis

NEUROLOGIC

- Porencephaly
- Hydrocephalus
- Cerebellar atrophy

Dysmorphic features/minor anomalies

- Hypertelorism, telecanthus
- Midface hypoplasia
- Broad nasal root, bifid nasal tip
- Microglossia

Other

- Short stature
- Conductive deafness
- Normal intelligence

Genetic test

None

Name: Otopalatodigital syndrome type 1

Synonyms:

Taybi syndrome

ICD 10 – BPA code	*Q870F*
ICD 9 – BPA-E*	759845
OMIM code	311300
ORPHA number	ORPHA669; 90650

Otopalatodigital syndrome type 1 (OPD1) is one of four otopalatodigital syndromes caused by mutations in *FLNA* gene (otopalatodigital syndrome types 1 and 2, frontometaphyseal dysplasia and Melnick-Needles syndrome). OPD1 is the mildest form of this phenotypic spectrum. Affected males have cleft palate, mild skeletal anomalies with conductive deafness caused by ossicular anomalies.

Associated major congenital anomalies

HEAD AND NECK
- Cleft palate
- Micrognathia

CARDIOVASCULAR
- Congenital heart disease

SKELETAL
- Pectus excavatum
- Scoliosis
- Hip dislocation
- Digital anomalies:
  - Short broad distal phalanx of the thumb
  - Overlengthening of the second toe and foreshortening of the great toe
  - Short and broad distal phalanges, especially thumbs
- Short third, fourth, fifth metacarpals, nonossified fifth metatarsal
- Short, broad halluces
- Syndactyly
- Camptodactyly
- Rocker-bottom feet

GENITOURINARY
- Hydronephrosis

NEUROLOGIC
- Hydrocephalus

Dysmorphic features/minor anomalies

- Frontal bossing
- Prominent supraorbital ridges, supraorbital hyperostosis
- Flat nasal bridge
- Hypertelorism
- Midface hypoplasia
- Microstomia
- Dental abnormalities

Other

- Short stature
- Conductive hearing loss

Genetic test

Detection of pathogenic variant in the filamin A gene (*FLNA*) (Xq28)

Name: Otopalatodigital syndrome type 2

Synonyms:

OPD II syndrome
OPD syndrome 2
Cranioorodigital syndrome
Faciopalatoosseous syndrome

ICD 10 – BPA code	*Q870F*
ICD 9 – BPA-E*	759845
OMIM code	304120
ORPHA number	ORPHA669; 90652

Otopalatodigital syndrome type 2 (OPD2) is a severe form of otopalatodigital syndrome spectrum disorder characterized by dysmorphic facies, severe skeletal dysplasia, and variable presence of extraskeletal anomalies of the brain, heart, genitourinary system, and intestine that frequently lead to perinatal death.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Hypomineralised calvaria in newborn
- Skull base scleosis
- Cleft palate
- Micrognathia

ABDOMINAL
- Omphalocele

GENITOURINARY
- Hypospadias
- Hydronephrosis

SKELETAL
- Pectus excavatum
- Thoracic hypoplasia
- Thin ribs
- Polydactyly
- Congenital hip dislocation
- Subluxation of elbows, wrists and knees
- Campomelia
- Anomalies of the hands and feet

NEUROLOGIC
- Hydrocephalus

Dysmorphic features/minor anomalies

- Prominent forehead
- Midface hypoplasia
- Hypertelorism
- Flat nasal bridge
- Small mouth
- Flexed overlapping fingers
- Hypoplastic, irregular metacarpals
- Poorly ossified phalanges of fingers and toes
- Bowing of long bones
- Crypotchidism

Other

- Short stature
- Conductive hearing loss
- Intellectual disability

Genetic test

Detection of pathogenic variant in the filamin A gene (*FLNA*) (Xq28)

Name: **Pena-Shokeir syndrome type 1**

Synonyms:

Fetal akinesia deformation sequence

Arthrogryposis multiplex congenita with pulmonary hypoplasia

ICD 10 – BPA code	Q878E
ICD 9 – BPA-E*	75989
OMIM code	208150; 300073
ORPHA number	ORPHA994

Pena-Shokeir syndrome type 1 is clinicaly and genetically heterogeneous constellation of features including fetal akinesia, intrauterine growth retardation, arthrogryposis, lung hypoplasia, cleft palate, and cryptorchdism.

Associated major congenital anomalies

HEAD AND NECK
- Cleft palate

RESPIRATORY
- Pulmonary hypoplasia

SKELETAL
- Multiple joint contractures
- Elbow and knee ankylosis
- Camptodactyly
- Rocker-bottom feet

NEUROLOGIC
- Hydrocephalus
- Microgyria
- Cerebellar hypoplasia

Dysmorphic features/minor anomalies

- Rigid, expressionless face
- Hypertelorism, telecanthus, ptosis
- Low set poorly folded, small, and posteriorly angulated ears
- Depressed tip of nose
- Long philtrum
- Microstomia
- Micrognathia
- Hypoplastic dermal ridges
- Cryptorchidism
- Absent septum pellucidum

Other

- Decreased fetal activity
- Intrauterine growth retardation
- Muscular atrophy

Genetic test

Detection of pathogenic variants in the 43-kD receptor-association protein of the synapse, gene *RAPSN* (11p11.2), in tyrosine kinase 7 gene *DOK7* (4p16.3), and in the skeletal muscle receptor tyrosine kinase gene *MUSK* (9q31.3)

Name: Pfeiffer syndrome

Synonyms:
Noack syndrome
Acrocephalosyndactyly type 5
ACS V

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	755501
OMIM code	101600
ORPHA number	ORPHA710

Pfeiffer syndrome is a form of acrocephalosyndactyly characterized by variable degrees of coronal craniosynostosis, hand and foot anomalies and various other associated manifestations. Based on severity, three subtypes of Pfeiffer syndrome are recognized, type 1, being the most common.

Associated major congenital anomalies

HEAD AND NECK
- Craniosynostosis (coronal with or without sagittal suture)
- Turribrachycephaly
- Clover-leaf skull (type II)

SKELETAL
- Broad thumbs and great toes
- Partial syndactyly of fingers and toes
- Brachymesophalangy of hands and feet

NEUROLOGIC
- Hydrocephalus
- Arnold-Chiari malformation

Dysmorphic features/minor anomalies

- Wide cranial vault
- Flat occiput
- Broad forehead
- Small nose with depressed nasal bridge
- Midface hypoplasia
- Hypertelorism, proptosis
- High arched palate
- Dental crowding
- Prognathia

Other

- Keratopathy
- Hearing impairment, conductive
- Laryngo-, tracheo-, bronchomalacia
- Obstructive sleep apnea
- Usually normal intelligence in type I
- Neurodevelopmental problems (type II and III)

Genetic test

Detection of pathogenic variant in the fibroblast growth factor receptor-2 gene *FGFR2* (10q26.13) gene or in the fibroblast growth factor receptor-1 gene *FGFR1* (8p11.23) gene in 80% patients

Name: Poland syndrome

Synonyms:
Poland anomaly
Poland sequence

ICD 10 – BPA code	Q7982
ICD 9 – BPA-E*	*756805*
OMIM code	173800
ORPHA number	ORPHA2911

Poland syndrome is characterized by a hypoplasia or absence of the pectoralis major muscle (most frequently involving the sternocostal portion) on one side of the body, and a variable degree of hand anomalies, including symbrachydactyly.

Associated major congenital anomalies

CARDIOVASCULAR
- Dextrocardia (if left-sided)

SKELETAL
- Unilateral hypoplasia or absence of pectoralis major/minor muscle
- Hypoplasia or absence of the muscles around the shoulder girdle
- Sprengel anomaly
- Hypoplastic ribs
- Fused ribs
- Unilateral hypoplasia or absence of nipple/breast
- Hemivertebrae
- Unilateral syndactyly/brachydactyly
- Unilateral oligodactyly

Dysmorphic features/minor anomalies

Other
- Möebius sequence

Genetic test
None

Name: Popliteal pterygium syndrome

Synonyms:

Facio-genito-popliteal syndrome

Popliteal web syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	756885
OMIM code	119500; 263650
ORPHA number	ORPHA1300; ORPHA1234

Popliteal pterygium syndrome is characterized by cleft lip, with or without cleft palate, contractures of the lower extremities, abnormal external genitalia, syndactyly of fingers and/or toes, and a pyramidal skin fold over the hallux nail.

Associated major congenital anomalies

HEAD AND NECK

- Congenital ankyloblepharon
- Cleft lip and/or palate in 91-97%
- Lower lip pits or sinuses in 45%

GENITOURINARY

- Hypoplastic vagina / uterus

SKELETAL

- Popliteal pterygium
- Intercrural pterygium
- Variable skin syndactyly fingers and toes
- Talipes equinovarus

Dysmorphic features/minor anomalies

- Bifid scrotum
- Hypoplastic scrotum
- Hypoplastic labia majora
- Spina bifida occulta
- Cryptorchidism

Other

- Pyramidal fold of skin overlying the nail of halux

Genetic test

Detection of pathogenic variant in the interferon regulatory factor 6 gene *IRF6* (1q32.2)

Name: Prader-Willi syndrome
Synonyms:
Willi-Prader syndrome
Prader-Labhart-Willi syndrome

ICD 10 – BPA code	Q8715
ICD 9 – BPA-E*	759872
OMIM code	176270; 615547
ORPHA number	ORPHA739

Prader-Willi syndrome is characterized by severe hypotonia during the neonatal period and first two years of life and the onset of hyperphagia with a risk of morbid obesity during infancy and adulthood, short stature, hypogonadotropic hypogonadism, and small hands and feet. Learning difficulties and behavioral problems or psychiatric problems.

Associated major congenital anomalies

SKELETAL
- Scoliosis
- Kyphosis

Dysmorphic features/minor anomalies

- Dolichocephaly
- Narrow bitemporal diameter
- Upslanting almond shaped palpebral fissures
- Thin upper lip, small, mouth, down-turned corners of mouth
- Small hands and feet
- Hypogenitalism: small penis, scrotal hypoplasia, hypoplastic labia minora/clitoris
- Cryptorchidism

Other

- Severe hypotonia in neonatal period and infancy
- Failure to thrive in infancy, onset of hyperphagia and obesity from 6 months to 6 years
- Strabismus
- Obstructive sleep apnea syndrome
- Osteoporosis, osteopenia
- Growth hormone deficiency
- Hypogonadotropic hypogonadism
- Learning disabilities
- Behavioural and psychiatric problems (temper tantrums, stubbornness, obsessive-

Genetic test

Detection of the lack of expression of the paternally derived PWS/AS region of chromosome 15q11.2-q13 by one of several genetic mechanisms (interstitial 15q11.2-q13 deletion (70%), maternal UPD (28%), imprinting defect or epimutation with or without deletion in the imprinting centre)

Name: Robinow-Silverman-Smith syndrome

Synonyms:

Robinow dwarfism
Fetal face syndrome
Acral dysostosis with facial and genital abnormalities
Mesomelic dwarfism-small genitalia syndrome

ICD 10 – BPA code	Q8716
ICD 9 – BPA-E*	75989
OMIM code	180700; 268310
ORPHA number	ORPHA3107; ORPHA1507; ORPHA97360

Robinow-Silverman-Smith syndrome is characterized by mesomelic limb shortening, dysmorphic features resembling a fetal face, hypoplastic external genitalia in males, and renal and vertebral anomalies Two forms of the syndrome with different patterns of inheritance and variable frequency of clinical signs have been described: a milder autosomal dominant form and severe autosomal recessive form.

Associated major congenital anomalies

HEART
- Right ventricular outlet obstruction

GENITOURINARY
- Renal anomalies in 27%

SKELETAL ABNORMALITIES
- Pectus excavatum
- Mesomelic limb shortening
- Vertebral segmentation defects
- Rib fusion in recessive form
- Brachydactyly
- Clinodactyly

Dysmorphic features/minor anomalies

- Macrocephaly
- Fetal face
- Frontal bossing
- Prominent, widely spaced eyes
- Midface hypoplasia
- Hypertelorism
- Broad/depressed nasal bridge, short upturned nose, anteverted nares
- Long philtrum
- Large mouth
- Abnormal uvula, crowded teeth
- Micrognathia
- Umbilical hernia
- Hypoplastic genitalia
- Cryptorchidism

Other

- Short stature (postnatal onset)
- Ear infections, Hearing loss
- Developmental delay/intellectual

Genetic test

Detection of pathogenic variants in *ROR2* gene (9q22) (AR variant) and in *WNT5A* gene (3p14.3) (AD variant)

Name: Rothmund-Thomson syndrome
Synonyms:
Poikiloderma Rothmund Thomson
Poikiloderma atroficans and cataract

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*757303*
OMIM code	268400
ORPHA number	ORPHA2909

Rothmund-Thomson syndrome is characterized by skin atrophy, telangiectasia, hyper- and hypopigmentation facial rash (poikiloderma), short stature, skeletal abnormalities, premature aging and a predisposition to malignancies.

Associated major congenital anomalies

HEAD AND NECK
- Juvenile zonular cataracts
- Microphthalmia
- Microcornea
- Mesodermal iris dysgenesis

ABDOMEN
- Annular pancreas

SKELETAL
- Kyphoscoliosis (in some patients)
- Congenital hip dislocation (rare)
- Forearm reduction defects
- Absence of patella
- Hypoplastic thumbs
- Club feet

Dysmorphic features/minor anomalies

- Sparse hair, eyelashes and/or eyebrows
- Frontal bossing
- Small nose, depressed nasal bridge
- Dental anomalies
- Prognathism
- Small hands and feet
- Cryptorchidism
-

Other

- Short stature
- Erythematous skin lesions in infancy, poikiloderma (atrophic plaques with telangiectasia), skin atrophy and sun sensitivity
- Premature aging
- Osteoporosis
- Hypogonadism
- Increased risk for malignoma
- Developmental delay/intellectual disability (some)

Genetic test

Detection of pathogenic variants in in *RECQL4* gene (8q24.3)

Name: Rubinstein-Taybi syndrome

Synonyms:

Broad thumb-hallux syndrome

Broad thumbs-halluces syndrome

ICD 10 – BPA code	*Q8723*
ICD 9 – BPA-E*	759841
OMIM code	180849; 610543; 613684
ORPHA number	ORPHA783; 353281; 353284

Rubinstein-Taybi syndrome is characterized by intellectual disability, short stature, specific facial dysmorphism (highly arched eyebrows, long eyelashes, downslanting palpebral fissures, beaked nose, high arched palate, micrognathia) congenital anomalies (microcephaly, broad thumbs and halluces) and characteristic grimacing or abnormal smile.

Associated major congenital anomalies

CARDIOVASCULAR

- Atrial septal defects
- Ventricular septal defects
- Patent ductus arteriosus
- Capillary hemangiomas
- Micrognathia

GENITOURINARY

- Hypospadias

SKELETAL

- Broad thumbs with radial angulation
- Broad great toes
- Syndactyly
- Polydactyly

Dysmorphic features/minor anomalies

- Highly arched eyebrows
- Long eyelashes
- Depressed nasal bridge and beaked nose
- Long hanging columella
- High arched palate
- Clinodactyly 5th finger
- Cryptorchidism

Other

- Short stature
- Unusual grimacing smile with complete closure of the eyes
- Keloid formation
- Common respiratory infections in infancy and childhood
- Constipation is a life-long problem
- Increased risk of tumors (leukemia, meningioma)
- Obsessive-compulsive behaviour
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in *CREBBP* gene (16p13.3) or in EP300 gene (22q13.2) or microdeletion 16p13.3

Name: Seckel syndrome
Synonyms:
Nanocephalic dwarfism
Bird-headed dwarfism

ICD 10 – BPA code	Q8718
ICD 9 – BPA-E*	759827
OMIM code	210600+ several
ORPHA number	ORPHA808

Seckel syndrome is characterized by a proportionate dwarfism of prenatal onset, a severe microcephaly with a bird-headed like appearance and intellectual disability.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly, severe
- Blepharophimosis
- Cleft palate
- Micrognathia

GENITOURINARY
- Hypospadias

SKELETAL
- Scoliosis
- Hip dislocation
- Hypoplasia of proximal radius
- Hypoplasia of proximal fibula
- Elbow flexion contracture

NEUROLOGIC
- Pachygyria
- Large basal ganglia
- Hypoplasia of the cerebellar vermis

Dysmorphic features/minor anomalies

- Sloping and narrow forehead
- Brid-like face
- Prominent eyes
- Large beaked nose
- Upward palpebral slanting
- Dental crowding
- Cryptorchidism
- Arachnoidal cysts

Other

- Short stature, proportionate
- Haemathological abnormalities
- Seizures
- Abnormalities of neuronal migration, such as heterotopias, or focal pachygyria or polymicrogyria
- Behavioural problems
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in *SCKL1* (3q22.1-q24, *ATR*), *SCKL2* (18q11.2, *RBBP8*), *SCKL5* (15q21.1, *CEP152*), *SCKL6* (3q22.2, *CEP63*) and *SCKL7* (14q22.1, *NIN*) genes

Name: Silver-Russell syndrome
Synonyms:
Silver's syndrome
Silver-Russel dwarfism

ICD 10 – BPA code	Q8717
ICD 9 – BPA-E*	759823
OMIM code	180860; 312780
ORPHA number	ORPHA813

Silver-Russel syndrome is characterized by severe intrauterine growth retardation, poor postnatal growth, characteristic triangular shaped face, limb asymmetry and a variety of minor anomalies.

Associated major congenital anomalies

HEAD AND NECK
- Micrognathia

CARDIOVASCULAR
- Cardiac defects

GENITOURINARY
- Posterior urethral valves
- Hypospadias

Dysmorphic features/minor anomalies

- Wide prominent forehead
- Triangular face
- Small, pointed chin
- Large eyes, bluish sclera
- Thin lips with downturn corners of the mouth
- Shortness and clinodactyly of the fifth finger
- Café au lait spots or skin pigmentary changes

Other

- Intrauterine growth retardation
- Proportionate short stature
- Failure to thrive
- Normal head circumference
- Limb, body, and/or facial asymmetry/hyperplasia
- Propensity to tumour development
- Hypoglycaemia
- Learning disabilities

Genetic test

Detection of :
- Loss of IC1 methylation of paternal 11p15.5 (~35%-50%)
- Duplication of maternal 11p15.5
- UPD 7(maternal) (~7%-10%),
- Chromosome 11p15 microduplication
- Chromosome 7p11.2p13 microduplication

Name: Sjögren-Larsson syndrome

Synonyms:

Fatty acid alcohol oxidoreductase deficiency

ICD 10 – BPA code	Q871A
ICD 9 – BPA-E*	75712
OMIM code	270200
ORPHA number	ORPHA816

Sjögren-Larsson syndrome is an inborn error of lipid metabolism caused by deficiency of fatty aldehyde dehydrogenase and characterized by congenital ichthyosis, intellectual deficit, spastic paraparesis, abnormality of retinal pigmentation, and leukoencephalopathy.

Associated major congenital anomalies

SKELETAL
- Thoracic kyphosis

Dysmorphic features/minor anomalies

Other
- Prematurity
- Short stature
- Generalized ichthyosis, pruritus
- Myopia, glistening white dotes in the retina of the eye, abnormality of retinal pigmentation
- Thickening of palmes and soles
- Spastic diplegia or less commonly tetraplegia
- Leukoencephalopathy
- Seizures in 40%
- Delayed speech, dysarthria
- Developmental delay/ intellectual disability

Genetic test

Detection of pathogenic variants in *ALDH3A2* gene (17p11.2)

Name: Smith-Lemli-Opitz syndrome

Synonyms:

7-dehydrocholesterol reductase deficiency
RSH syndrome
SLOS

ICD 10 – BPA code	Q8719
ICD 9 – BPA-E*	759828
OMIM code	270400
ORPHA number	ORPHA818

Smith-Lemli-Opitz syndrome is an inborn error of lipid metabolism due to deficiency of 7-dehydrocholesterol reductase and characterized by multiple congenital anomalies (microcephaly, incomplete development of the male genitalia), dysmorphic face, intellectual deficit and behavioural problems.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Ptosis
- Cataract
- Cleft palate

CARDIOVASCULAR
- Ventricular septal defect
- Atrial septal defect
- Coarctation of aorta
- Patent ductus arteriosus

GENITOURINARY
- Hypospadias
- Ambiguous genitalia
- Renal agenesis
- Hydronephrosis
- Cystic kidneys
- Ureteropelvic junction obstruction

SKELETAL
- Hip dislocation
- Short limbs
- Postaxial polydactyly of the hands and feet
- Proximally placed, short thumbs and toes

NEUROLOGICAL
- Hypoplasia or agenesis of corpus callosum
- Cerebellar hypoplasia
- Holoprosencephaly
- Hydrocephalus
- Frontal lobe hypoplasia

Dysmorphic features/minor anomalies

- Micrognathia
- Anteverted nares
- Broad, flat nasal bridge
- Micropenis, hypoplastic scrotum, bifid scrotum, , cryptorchidism

Other

- Short stature
- Failure to thrive
- Elevated 7-dehydrocholesterol in serum and tissues, low cholesterol
- Seizures
- Behavioural problems
- Developmental delay/ intellectual disability

Genetic test

Detection of pathogenic variants in the delta-7-dehydrocholesterol reductase gene *DHCR7* (11q13.4)

Name: Smith-Magenis syndrome
Synonyms:
17p11.2 microdeletion syndrome

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*75989*
OMIM code	182290
ORPHA number	ORPHA819

Smith-Magenis Syndrome is characterized by distinctive dysmorphic features (brachycephaly, a broad square-shaped face, hypertelorism, synophrys, upslanting palpebral fissures, midface hypoplasia with depressed nasal bridge, bowed upper lip) that progress with age, mild to moderate developmental delay/intellectual disability, and behavioural abnormalities including significant sleep/wake circadian rhythm disorders, hyperactivity, attention deficit, aggressive and self-injurious activities.

Associated major congenital anomalies

HEAD AND NECK
- Micrognathia

CARDIOVASCULAR
- Congenital heart defect

GENITOURINARY
- Structural renal anomalies

SKELETAL
- Scoliosis
- Brachydactyly

Dysmorphic features/minor anomalies

- Brachicephaly
- Frontal bossing
- Synophris
- Deep-set eyes
- A broad square-shaped face with depressed nasal bridge
- Midface retrusion
- Everted, "tented"vermilion of the upper lip

Other

- Failure to thrive in infancy
- Hearing loss (conductive and/or sensorineural)
- Obesity in adults
- Insensitivity to pain
- Speech delay
- Sleep disorders
- Behavioural problems
- Autism spectrum disroder
- Developmental delay/ intellectual disability

Genetic test

Detection of interstitial deletion of 17p11.2 (25 genes, *RAI1* gene is most important for clinical features)

Name: Sotos syndrome
Synonyms:
Cerebral gigantism

ICD 10 – BPA code	Q8731
ICD 9 – BPA-E*	756883
OMIM code	117550; 617169
ORPHA number	ORPHA821

Sotos syndrome is a rare multisystemic genetic disorder characterized by a typical facial appearance, overgrowth of the body in early life with macrocephaly, and mild to severe intelectual disability.

Associated major congenital anomalies

CARDIOVASCULAR
- Atrial septal defect
- Ventricular septal defect
- Patent ductus arteriosus

SKELETAL
- Genu valgum

NEUROLOGIC
- Partial to complete agenesis of corpus callosum
- Persistent cavum septum pellucidum
- Large cisterna magna
- Ventriculomegaly
- Prominent trigone and occipital horns

Dysmorphic features/minor anomalies

- Macrocephaly, dolichocephaly
- Broad and prominent forehead
- Sparse frontotemporal hair
- Downslanting palpebral fissures
- Malar flushing
- Long and narrow face
- Long chin
- Pes planus
- Large hands and feets

Other

- Overgrowth
- Advanced bone age
- Joint hyperlaxity
- Seizures
- Behavioural problems
- Learning difficulties
- Developmental delay/intellectual disability

Genetic test

Microdeletion 5q35.2-q35.3 or detection of pathogenic variants in the nuclear receptor binding SET domain protein 1 gene *NSD1*

Name: **Stickler syndrome**

Synonyms:

Hereditary progressive arthroophthalmopathy

ICD 10 – BPA code	Q8709
ICD 9 – BPA-E*	*75989*
OMIM code	108300; 604841; 184840
ORPHA number	ORPHA828; 90653; 90654; 166100

Stickler syndrome characterized by association of ocular, auditory, skeletal, and orofacial abnormalities.

Associated major congenital anomalies

HEAD AND NECK

- Cataract
- Cleft palate
- Pierre Robin sequence
- Micrognathia

CARDIOVASCULAR

- Mitral valve prolapse

SKELETAL

- Pectus excavatum
- Mild spondyloepiphyseal dysplasia
- Platyspondyly with anterior wedging
- Scoliosis
- Kyphosis

Dysmorphic features/minor anomalies

- Malar hypoplasia
- Retrognathia
- Arachnodactyly

Other

- Marfanoid habitus
- Myopia, retinal detachment, blindness
- Sensorineural/conductive hearing loss
- Joint hypermolbility
- Arthropathy Slipped epiphysis or Legg-Perthes-like disease

Genetic test

Detection of pathogenic variants in genes: *COLA2A1* (12q13.11) (Type 1), *COL11A1* (1p21.1) (Type 2), *COL11A2* (6p21.32) (Type 3) and *COL9A1*

Name: Sturge-Weber syndrome

Synonyms:

Encephalofacial angiomatosis
Encephalotrigeminal angiomatosis
Sturge-Weber-Dimitri syndrome

ICD 10 – BPA code	Q8581
ICD 9 – BPA-E*	759611
OMIM code	185300
ORPHA number	ORPHA3205

Sturge-Weber syndrome is phakomatosis characterized by facial cutaneous vascular malformation (port-wine stain) in combination with ocular and/or intracranial vascular anomaly leading commonly to seizures and glaucoma.

Associated major congenital anomalies

HEAD AND NECK

- Port wine stain in at least first branch (ophthalmic) of trigeminal nerve distribution, unilateral, occasionally bilateral

NEUROLOGIC

- Leptomeningeal angiomatosis
- Cerebral cortical atrophy

Dysmorphic features/minor anomalies

- Macrocephaly

Other

- Glaucoma, buphtalmos
- Seizures
- Headache
- Stroke-like episodes
- Hemiparesis, hemianopsia
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variant in GNAQ gene (9q21): c.548G>A in 88% cases

Name: TAR syndrome

Synonyms:

Thrombocytopenia-absent radius syndrome

ICD 10 – BPA code	Q8725
ICD 9 – BPA-E*	*75526*
OMIM code	274000
ORPHA number	ORPHA3320

Thrombocytopenia-absent radius (TAR) syndrome is characterized by thrombocytopenia and absence of the radius Thumbs are always present.

Associated major congenital anomalies

CARDIAC ANOMALIES

- Atrial septal defect
- Ventricular septal defect
- Patent arterial duct
- Tetralogy of Fallot

SKELETAL

- Bilateral absence of the radius with present thumbs
- Hypoplasia or unilateral/bilateral absence of ulna
- Abnormal humerus
- Dislocation of the joints
- Phocomelia in the most severe cases

NEUROLOGIC

- Hypoplasia of cerebellum
- Cavum septum pellucidum
- Absence of the corpus callosum

Dysmorphic features/minor anomalies

- Brachycephaly
- Small, upturned nose
- Micrognathia

Other

- Thrombocytopenia
- Hypogammaglobulinemia
- Intellectual deficit in less than 10%

Genetic test

Detection of deletion on chromosome 1q21.1 or pathogenic variant in *RBM8A* gene

Name: Treacher-Collins syndrome

Synonyms:

Franceschetti-Klein syndrome
Mandibulofacial dysostosis without limb anomalies

ICD 10 – BPA code	Q754/Q870A
ICD 9 – BPA-E*	756041
OMIM code	154500; 248390; 613717
ORPHA number	ORPHA861

Treacher Collins syndrome is a congenital disorder of craniofacial development characterized by bilateral symmetrical hypoplasia of the zygomatic bones and mandible. The features include antimongoloid slant of the eyes, coloboma of the eyelid, micrognathia, microtia and other deformity of the ears, and macrostomia. Conductive hearing loss and cleft palate are often present.

Associated major congenital anomalies

HEAD AND NECK

- Bilateral and symmetrical hypoplasia of the malar bones and infra-orbital rim (80% of cases) and of the mandibule (70% of cases)
- Coloboma of the lower eyelid
- Anotia
- Atresia of external auditory canal
- Anomalies of ossicular chain
- Complex abnormalities of temporo-mandibular joints
- Choanal stenosis/atresia
- Cleft palate
- Micrognathia

Dysmorphic features/minor anomalies

- Macrocephaly
- Antimongoloid position of palpebral fissures (89%)
- Microtia
- High-arched palate
- Macrostomia
- Dental anomalies
- Preauricular hair displacement onto the cheeks

Other

- Conductive hearing loss
- Breathing and nutritional difficulties
- Intelligence is usually normal

Genetic test

Detection of pathogenic variant in the Treacle - TCOF1 gene, (5q32), in the polymerase I, RNA, subunit C gene POLR1C gene (6p21.1) or polymerase I, RNA, subunit D gene POLR1D (13q12.2) gene.

Name: Trichorhinophalangeal syndrome type I and III

Synonyms:
Sugio:Kajii syndrome (type III)

ICD 10 – BPA code	*Q870B*
ICD 9 – BPA-E*	*75989*
OMIM code	190350; 190351
ORPHA number	ORPHA77258

Trichorhinophalangeal syndromes type 1 and type 3 are characterized by distinctive craniofacial and skeletal abnormalities. Dysmorphic features include sparse hair, bulbous nasal tip, long flat philtrum, thin upper lip, and protruding ears. Skeletal anomalies include brachydactyly, cone-shaped epiphyses at the phalanges, hip anomalies, and short stature.

Associated major congenital anomalies

HEAD AND NECK

- Micrognathia

SKELETAL

- Pectus carinatum
- Scoliosis
- Lordosis
- Short metacarpals and metatarsals
- Brachydactyly
- Cone-shaped epiphyses of middle and proximal phalanges

Dysmorphic features/minor anomalies

- Sparse hair, thin eyebrows
- Frontal bossing
- Long protruding ears
- Pear-shaped nose
- Prominent philtrum
- Thin upper lip
- Dental anomalies
- Thin nails
- Clinodactyly of the 5th finger
-

Other

- Short stature
- No exostoses
- Delayed bone age before puberty
- Accelerated bone age after puberty
- No intellectual deficit

Genetic test

Detection of pathogenic variant in the zinc finger transcription factor *TRPS1* (8q24.12)

Name: Van der Woude syndrome

Synonyms:

Cleft lip/palate with mucous cysts of lower lip,
Lip-pit syndrome
VWS

ICD 10 – BPA code	*Q878*
ICD 9 – BPA-E*	*75989*
OMIM code	119300; 604547; 606713
ORPHA number	ORPHA888

Van der Woude syndrome is characterized by the combination of lower lip pits and/or sinuses, cleft lip with or without cleft palate, and cleft palate alone.

Associated major congenital anomalies

HEAD AND NECK

- Cleft lip with or without cleft palate
- Hypodontia

SKELETAL

- Syndactyly of the hands

Dysmorphic features/minor anomalies

- Cleft uvula
- Paramedian lower lip pits in 80%

Other

- Same pathogenic variants can cause the popliteal pterygium syndrome. Both disorders have been observed in the same family.

Genetic test

Detection of pathogenic variant in the interferon regulatory factor 6 gene *IRF6* (1q32.2) in 68% of cases

Name: Velocardiofacial syndrome

Synonyms:

22q11 deletion syndrome, CATCH 22, Conotruncal anomaly face syndrome, DiGeorge syndrome, DiGeorge sequence, Microdeletion 22q11.2, Monosomy 22q11, Shprintzen syndrome

ICD 10 – BPA code	D821
ICD 9 – BPA-E*	27910
OMIM number	188400; 192430
ORPHA code	ORPHA567

Velocardiofacial syndrome is a chromosomal anomaly which causes a congenital malformation disorder whose common features include cardiac defects, palatal anomalies, facial dysmorphism, developmental delay and immune deficiency.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly in 40-50%
- Craniosynostosis
- Coloboma
- Cataract
- Cleft palate
- Absent/hypoplastic thymus
- Parathyroid hypoplasia

CARDIOVASCULAR

Conotruncl heart defects
- Truncus arteriosus
- Ventricular septal defect
- Right aortic arch
- Tetralogy of Fallot
- Interrupted aortic arch
- Double aortic arch

ABDOMINAL
- Esophageal atresia
- Diaphragmatic hernia
- Hirschsprung disease

GENITOURINARY
- Renal agenesis
- Horseshoe kidney
- Hydronephrosis
- Multicystic/dysplastic kidneys
- Absent uterus
- Hypospadia

SKELETAL
- Hemivertebrae
- Polydactyly of hands and feet

Dysmorphic features/minor anomalies

- Narrow palpebral fissures, Eyelid hooding
- Minor auricular anomalies
- Prominent nose with squared nasal root, hypoplastic nasal alae, bulbou nasal tip
- High-arched palate
- Retruded mandible with chin deficiency
- Inguinal hernia
- Slender hands and digits

Other
- T-cell deficiency, recurrent infections
- Hypocalcemia
- Hypothyroidism
- Feeding difficulties
- Velopharyngeal insufficiency
- Hearing loss
- Autoimmune disease (Graves, rheumatoid arthritis)
- Growth hormone deficiency
- Psychiatric disorders
- Autism
- Learning difficulties
- Developmental delay/intellectual disability

Genetic test

Detection of 22q11.21 deletion

Name: Weaver syndrome

Synonyms:

Camptodactyly-overgrowth-unusual facies syndrome

ICD 10 – BPA code	Q8732
ICD 9 – BPA-E*	*75989*
OMIM code	277590
ORPHA number	ORPHA3447

Weaver syndrome is multisystemic, mostly sporadic and genetically heterogeneous syndrome characterized by overgrowth, typical facial appearance with hypertelorism and retrognathia, and variable intellectual disability. Additional features may include camptodactyly, soft doughy skin, umbilical hernia, and a low hoarse cry.

Associated major congenital anomalies

SKELETAL

- Pectus excavatum
- Scoliosis
- Kyphosis
- Coxa valga
- Limited extension of elbow and knee
- Camptodactyly
- Clinodactily
- Talipes equinovarus

Dysmorphic features/minor anomalies

- Macrocephaly
- Flattened occiput
- Broad forehead
- Round face (young children)
- Hypertelorism, epicanthus, downslanting palpebral fissures
- Large fleshy ears
- Retrognathia, prominent horizontal chin crease
- Large hands
- Umbilical hernia
- Cryptorchidism

Other

- Increased prenatal and postnatal growth
- Tall stature
- Coarse, low-pitched voice
- Loose skin
- Accelerated osseus maturation
- Higher risk of neuroblastoma
- Growth hormone deficiency in adults
- Hypertonia/hypotonia
- Mild intellectual disability

Genetic test

Detection of pathogenic variants in Drosophila enhancer of zeste (*EZH2*) gene (7q35-q36).
Some cases due to pathogenic variants in *NSD1* gene

Name: Weill-Marchesani syndrome

Synonyms:

Spherophakia-brachymorphia syndrome
Congenital mesodermal dysmorphodystrophy
Marchesani -Weill syndrome

ICD 10 – BPA code	*Q875*
ICD 9 – BPA-E*	*759897*
OMIM code	277600; 608328; 614819
ORPHA number	ORPHA3449

Weill-Marchesani syndrome is a connective tissue disorder characterized by by abnormalities of the lens of the eye, proportionate short stature, brachydactyly, and joint stiffness.

Associated major congenital anomalies

HEAD AND NECK

Eye anomalies

- Microspherophakia
- Cataract
- Ectopia of the lens

CARDIOVASCULAR

- Ventricular septal defect
- Mitral valve insufficiency
- Aortic valve stenosis
- Pulmonary valve stenosis
- Ductus arteriosus

SKELETAL

- Scoliosis
- Brachydactyly
- Broad phalanges
- Broad metacarpals/ metatarsals
- Joint stiffness

Dysmorphic features/minor anomalies

- Brachycephaly
- Small shallow orbits
- Maxillary hypoplasia
- Depressed nasal bridge
- Narrow palate

Other

- Short stature, proportionate
- Severe myopia, blindness, glaucoma
- Thick skin
- Muscular build
- Mild developmental delay (13%)

Genetic test

Detection of pathogenic variants in a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 10 gene (*ADAMTS10*) (19p13.2) or in the fibrillin-1 gene *FBN1* (15q21.1)

Name: Whistling face syndrome

Synonyms:

Freeman-Sheldon syndrome
Distal arthrogryposis type 2A
Craniocarpotarsal dysplasia

ICD 10 – BPA code	Q870C
ICD 9 – BPA-E*	759807
OMIM code	193700; 277720; 616266
ORPHA number	ORPHA2053

Whistling face syndrome is characterized by a distinctive face that includes microstomia with a whistling appearance of the mouith puckered lips, and an H-shaped dimple of the chin; and distal atrthrogryposis presentig with joint contractures and clubfoot.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Blepharophimosis
- Micrognathia

SKELETAL
- Kyphoscoliosis
- Contractures (distal arthrogryposis)
- Ulnar deviation of hands
- Camptodactyly
- Pes equinovarus

Dysmorphic features/minor anomalies

- Mask-like facies with small mouth
- Deep-set eyes, blepharphymosis
- Hypoplastic alae nasi
- Long philtrum
- Full cheeks
- Small pursed mouth, whistling appearece
- H shaped chin creases
- Dental crowding

Other

- Failure to thrive
- Breech position
- Malignant hypertermia
- Learing difficulties

Genetic test

Detection of pathogenic variants in the embryonic skeletal muscle myosin heavy chain 3 gene *MYH3* (17p13.1)

Name: Williams syndrome

Synonyms:

Williams-Beuren syndrome
Deletion 7q11.23
Monosomy 7q11.23

ICD 10 – BPA code	Q8784
ICD 9 – BPA-E*	*75989*
OMIM code	194050
ORPHA number	ORPHA904

Williams syndrome is multisystemic neurodevelopmental disorder caused by haploinsufficiency of 1.5 to 1.8 Mb on chromosome 7q11.23. It is characterized by a distinct facial appearance, cardiovascular defects, connective tissue abnormalities, learning difficulties and characteristic behavioural phenotype.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Hypodontia

CARDIOVASCULAR
- Supravalvular aortic stenosis
- Peripheral pulmonary artery stenosis
- Pulmonic valvular stenosis
- Septal defects
- Mitral valve prolaps

GENITOURINARY
- Renal agenesis
- Pelvic kidney
- Nephorcalcinosis

SKELETAL
- Pectus excavatum
- Joint contractures

Dysmorphic features/minor anomalies

- Elfin face
- Broad forehead, bitemporal narrowing
- Periorbital fullness, epicanthus, stellate/lacy pattern of iris
- Large ears
- Depressed nasal bridge, short nose, anteverted nares
- Long philtrum
- Full lips, large mouth
- Microdontia, enamel hypoplasia
- Inguinal hernia

Other

- Short stature
- Hearing loss/hyperacusis
- Gastroesophageal reflux
- Hypertension
- Joint laxity
- Endocrine abnormalities
- Hypercalcemia in infancy
- Specific cognitive profile
- Friendly outgoing personality
- Intellectual disability, relative sparing of language

Genetic test

Detection of deletion 7q11.23

Name: Zellweger syndrome
Synonyms:
Cerebro-hepato-renal syndrome
ZS

ICD 10 – BPA code	Q8783
ICD 9 – BPA-E*	759875
OMIM code	214100 + several
ORPHA number	ORPHA912

Zellweger syndrome (ZS) is the most severe form of peroxisome biogenesis disorders characterised by absence or reduced numbers of peroxisomes in tissues as well as multiple enzyme abnormalities. It is characterized by neuronal migration defects in the brain, dysmorphic craniofacial features, profound hypotonia, neonatal seizures, and liver dysfunction.

Associated major congenital anomalies

HEAD AND NECK
- Turribrachycephaly
- Corneal opacity
- Congenital cataract
- Hypoplastic optic disc

CARDIOVASCULAR
- Patent ductus arteriosus
- Septal defects

GASTROINTESTINAL
- Liver cysts

GENITOURINARY
- Hypospadias
- Cryptorchidism
- Hydronephrosis
- Renal corticall small cysts

SKELETAL
- Stippled epiphyses
- Variable contractures with camptodactily
- Equinovarus deformity
- Triradiate cartilages

NEUROLOGIC
- Pachymicrogyria
- Heterotopias/Abnormal migration
- Subependymal cysts
- Hypoplastic corpus callosum
- Hypoplastic olfactory lobes

Dysmorphic features/minor anomalies

- Macrocephaly
- Large anterior fontanel
- Flattened occiput
- High forehead
- Flat face
- Upslanting palpebral fissures, epicanthus
- Broad nasal bridge, anteverted nares
- High-arched palate

Other

- Failure to thrive
- Loss of vision
- Hearing loss
- Hepatomegaly, hepatic failure, jaundice, coagulopathy
- Variable elevated serum iron level
- Evidence of excess iron storage
- Pipecolic acidemia
- Abnormal bile acids
- Accumulation of very long-chain fatty acids
- Hypotonia
- Seizures
- Developmental delay/intellectual disability

Genetic test

Detection of pathogenic variants in one of the 13 *PEX* genes encoding peroxins

Teratogenic syndromes

Name: Fetal alcohol syndrome

Synonyms:

ARBD, ARND
Alcohol related birth defects
Alcohol related neurodevelopmental disorder
FAS, Fetal alcohol spectrum disorders

ICD 10 – BPA code	Q860
ICD 9 – BPA-E*	76076
OMIM code	-
ORPHA number	ORPHA1915

Fetal alcohol syndrome is caused by excessive maternal consumption of alcohol during pregnancy. Clinical manifestations include characteristic facial features, prenatal and/or postnatal growth deficiency and neurologic abnormalities such as microcephaly, developmental disabilities nad behavioural disturbances.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Ptosis
- Cleft lip/palate (some)

CARDIOVASCULAR
- Ventricular septal defects
- Arterial septal defects

GENITOURINARY
- Hypospadias
- Small kindeys
- Hydronephrosis

SKELETAL ANOMALIES
- Pectus excavatum
- Limited joint movements (fingers, elbows)

NEUROLOGIC
- Cerebral and cerebellar volume reduction
- Abnormalities of corpus callosum

Dysmorphic features/minor anomalies

- Short palpebral fissures, epicanthus
- Maxillary hypoplasia
- Short upturned nose
- Long and smooth philtrum
- Thin upper lip
- Micrognathia
- Small fifth fingernails
- Small distal phalanges

Other

- Prenatal and/or postnatal growth deficiency
- Hyperacitivity/attention deficit
- Intellectual disability
- Learning difficulties

Name: Fetal Cytomegalovirus (CMV) syndrome

Synonyms:

Antenatal CMV infection

Antenatal citomegalovirus infection

ICD 10 – BPA code	P351
ICD 9 – BPA-E*	77110
OMIM code	-
ORPHA number	ORPHA294

Congenital cytomegalovirus infection is a fetopathy that is likely to occur when a CMV-infected pregnant woman transmits the virus to the fetus through the placenta.

Associated major congenital anomalies

HEAD AND NECK

- Microcephaly

NEUROLOGICAL

- Intracranial calcifications

Dysmorphic features/minor anomalies

Other

- Fetal growth retardation
- Sensorineural hearing loss
- Seizures
- Chorioretinits
- Hepato- and splenomegaly
- Hematological abnormalities
- Petechial rash
- Intellectual and motor disabilities

Name: Fetal hydantoin syndrome
Synonyms:
Phenytoin embryofetopathy

ICD 10 – BPA code	Q861
ICD 9 – BPA-E*	*7607*
OMIM code	-
ORPHA number	ORPHA:1912

Fetal hydantoin syndrome is a drug-related embryofetopathy that can occur when an embryo/fetus is exposed to anticonvulsant drug hydantoin (phenytoin, diphenylhydantoin).

Associated major congenital anomalies

HEAD AND NECK
- Abnormality of the fontanelles or cranial sutures
- Microcephaly
- Ptosis
- Cleft lip/palate

CARDIOVASCULAR
- Ventricular septal defect

SKELETAL
- Hypoplastic distal phalanges

Dysmorphic features/minor anomalies

- Hypertelorism
- Epicanthal folds
- Depressed nasal bridge
- Short upturned nose
- Low-set, posteriorly rotated ears
- Wide mouth with prominent lips
- Bowed upper lip
- Short neck
- Umbilical and inguinal hernias
- Hypoplastic nails

Other

- Prenatal and postnatal growth retardation
- Cognitive deficits and developmental delay
- Sensorineural hearing impairment

Name: Fetal Rubella syndrome

Synonyms:

CRS

Congenital rubella syndrome

ICD 10 – BPA code	P350
ICD 9 – BPA-E*	*7710,* or *7602*
OMIM code	-
ORPHA number	ORPHA290

Fetal rubella syndrome is an infectious embryofetopathy that may present in an infant as a result of maternal infection and subsequent fetal infection with rubella virus.

Associated major congenital anomalies

HEAD AND NECK

- Microcephaly
- Cataracts
- Microphthalmia
- Micrognathia

CARDIOVASCULAR

- Peripheral pulmonary artery stenosis
- Patent ductus arteriosus

Congenital heart defects

- Ventricular septal defects
- Tetralogy of Fallot

Dysmorphic features/minor anomalies

Other

- Intrauterine growth retardation
- Low brith weight
- Sensorineural deafness
- Glaucoma
- Chorioretinitis
- Developmental delay/intellectual disability

Name: Fetal thalidomide syndrome
Synonyms:
Thalidomide embryopathy

ICD 10 – BPA code	Q8682
ICD 9 – BPA-E*	*7607*
OMIM code	-
ORPHA number	ORPHA3312

Fetal thalidomide syndrome is a group of anomalies presented in infants as a result of in utero exposure (between 35 and 50 days after fertilization) to thalidomide.

Associated major congenital anomalies

HEAD AND NECK
- Anotia
- Microphthalmia
- Anophtalmus
- Coloboma
- Orofacial clefts

CARDIOVASCULAR
- Congenital cardiac anomalies
- Atrial septal defect
- Ventricular septal defect
- Pulmonary stenosis
- Tetralogy of Fallot

ABDOMINAL
- Esophageal and duodenal atresia

GENITOURINARY
- Renal agenesis/dysgenesis

SKELETAL
- Phocomelia
- Amelia
- Forelimb and hand anomalies

Dysmorphic features/minor anomalies

- Preauricular skin tags
- Microtia

Other

- Growth retardation
- Facial hemangiomas
- Strabismus
- Congenital facial palsy

Name: Fetal Toxoplasmosis

Synonyms:

Congenital toxoplasmosis
Toxoplasma embryofetopathy
Toxoplasma embryopathy

ICD 10 – BPA code	P371
ICD 9 – BPA-E*	77121
OMIM code	-
ORPHA number	ORPHA858

Fetal toxoplasmosis is an embryofetopathy characterized by ocular, visceral or intracranial lesions secondary to maternal primo infection by *Toxoplasma gondii.*

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly

NEUROLOGICAL
- Intracranial calcifications
- Hydrocephalus
- Ventricular dilatation

Dysmorphic features/minor anomalies

Other
- Chorioretinitis
- Hepato- and splenomegaly
- Cardiomegaly
- Ascites
- Hematological abnormalities
- Intrauterine growth retardation
- Develompental delay
- Seizures

Name: Fetal valproate syndrome

Synonyms:

Fetal valproic acid syndrome

ICD 10 – BPA code	Q868
ICD 9 – BPA-E*	*7607*
OMIM code	-
ORPHA number	ORPHA1906

Fetal valproate syndrome is an anticonvulsant drug-related embryofetopathy that can occur when a fetus is exposed to valproic acid, characterized by distinct facial dysmorphism, congenital anomalies and developmental delay specially in language and communication.

Associated major congenital anomalies

HEAD AND NECK
- Cleft lip/palate

CARDIOVASCULAR

Congenital heart defects
- Ventricular septal defects
- Hypoplastic left heart
- Aortic/pulmonary stenosis

GENITOURINARY
- Hypospadias

SKELETAL
- Absence of the first rib
- Finger and hand contractures
- Joint hyperlaxity
- Clubfoot

NEUROLOGICAL
- Neural tube defects

Dysmorphic features/minor anomalies

- High/broad forehead with bifrontal narrowing
- Metopic craniosynostosis
- Lateral deficiency of eyebrows
- Hypertelorism, epicanthal folds
- Infraorbital groove
- Small/broad upturned nose
- Long and shallow philtrum
- Thin upper lip, thick lower lip
- Cryptorchidism

Other

- Myopia
- Tracheomalacia
- Developmental delay
- Learning disabilities and/or communication problems
- ADHD
- Autism spectrum disorder

Name: Fetal warfarin syndrome

Synonyms:

Coumarin embryopathy

Vitamin K antagonists embryofetopathy

ICD 10 – BPA code	Q862
ICD 9 – BPA-E*	*7607*
OMIM code	-
ORPHA number	ORPHA1914

Fetal warfarin syndrome is characterized by a group of symptoms that may be observed in a fetus or newborn when the mother was taken warfarin (vitamin K antagonist) during pregnancy.

Associated major congenital anomalies

HEAD AND NECK

- Microcephaly
- Microphthalmia
- Cataract
- Optic atrophy
- Choanal atresia
- Cleft lip/palate

CARDIOVASCULAR

Congenital heart defects

GENITOURINARY

- Renal agenesis

SKELETAL

- Pectus carinatum
- Short limbs
- Stippled epiphyses
- Brachydactyly

NEUROLOGIC

- Hydrocephalus/Ventriculomegaly
- Agenesis of corups callosum
- Dandy Walker malformation

Dysmorphic features/minor anomalies

- Malformed ears
- Nasal hypoplasia (nose sunken into face)
- Hypoplasia of nails

Other

- Growth retardation
- Hearing loss
- Laryngomalacia
- Spasticity
- Seizures
- Intellectual disability
- *Situs inversus* totalis

Name: **Fetal zika virus syndrome**
Synonyms:

ICD 10 – BPA code	P354
ICD 9 – BPA-E*	-
OMIM code	-
ORPHA number	ORPHA 448237

Fetal yika virus syndrome is a pattern of congenital anomalies found among fetuses and babies infected with Aedes mosquito-born Zika virus during pregnancy. Congenital zika syndrome is described by the following five features: severe microcephaly, ocular changes, joint contractures and hypertonia.

Associated major congenital anomalies

HEAD AND NECK
- Microcephaly
- Bilateral macular and perimacular lesions as well as optic nerve abnormalities

SKELETAL
- Fetal akinesia deformation sequence (ie, arthrogryposis)

NEUROLOGICAL
- Ventriculomegaly
- Cerebellar hypoplasia
- Hydrocephalus with, lissencephaly

Dysmorphic features/minor anomalies

- Malformed ears
- Nasal hypoplasia (nose sunken into face)

Other

- Hearing loss
- Spasticity
- Seizures
- Developmental delay

Skeletal dysplasias

Name: Achondrogenesis type 1A and 1B

Synoyms:

Achondrogenesis type 1A, Houston-Harris type

Achondrogenesis type 1B, Parenti-Fraccaro type

ICD 10 – BPA code	Q7700
ICD 9 – BPA-E*	*75644*
OMIM code	200600; 600972
ORPHA number	ORPHA932, 93299,93298

Achondrogenesis type 1A and 1B are form of achondrogenesis a very rare, lethal skeletal dysplasia characterized by extremely short stature with short limbs, narrow chest, soft skull bones, and distinctive histological features of the cartilage. Type 1A is characterized by short trunk with prominent abdomen, hydropic appearance, short ribs that are easily fractured and the proximal femora with metaphyseal spikes. In type 1B rib fractures do not occur and the distal femora have metaphyseal irregularities.

Associated major congenital anomalies

HEAD AND NECK
- Poorly ossified skull

SKELETAL
- Barrel shaped chest
- Short, fractured ribs (type I)
- Short, wide clavicles
- Hypoplastic scapulae
- Micromelia, flipper-like arms and legs
- Short broad tibia
- Short radius
- Clubfoot

NEUROLOGICAL
- Encephalocele

Dysmorphic features/minor anomalies

- Macrocephaly
- Chubby cheeks
- Flat nasal bridge, short nose, anteverted nares
- Small mouth
- Umbilical hernia

Other

- Short stature
- Fetal hydrops
- Polyhydramnios

Genetic test

Detection of pathogenic variant in *TRIP11* gene (14q32.12) for type 1A and in *SLC26A2* gene (5q32) for type 1B

Name: Achondrogenesis type 2

Synonyms:

Achondrogenesis, Langer-Saldino type
Chondrogenesis imperfecta
Hypochondrogenesis (Q7702)

ICD 10 – BPA code	Q7701/ Q7702
ICD 9 – BPA-E*	*75644*
OMIM code	200610
ORPHA number	ORPHA93296

Achondrogenesis type 2 is a form of achondrogenesis and is a very rare severe and lethal skeletal dysplasia and part of the spectrum of type 2 collagen-related bone disorders. It is characterized by short trunk with prominent abdomen and striking micromelia.

Associated major congenital anomalies

HEAD AND NECK
- Cleft palate

CARDIOVASCULAR
- Atrial septal defect
- Atrioventricular canal defect

SKELETAL
- Narrow chest
- Short trunk
- Short ribs
- Normal clavicles
- Micromelia
- Very short, broad tubular bones
- Flared, cupped metaphyses

Dysmorphic features/minor anomalies

- Enlarged calvaria with normal ossification
- Prominent forehead
- Small chin

Other

- Prematurity
- Fetal hydrops
- Extreme short stature
- Protuberant abdomen
- Fetal hydrops
- Polyhydramnios
- Distinctive histological features of cartilage

Genetic test

Detection of pathogenic variant in *COL2A1* gene (12q13.11)

Name:
Achondroplasia/hypochondroplasia
Synonyms:

ICD 10 – BPA code	Q774
ICD 9 – BPA-E*	75643
OMIM code	100800
ORPHA number	ORPHA15

Achondroplasia is the most common form of chondrodysplasia, characterized by short-limb dwarfism, rhizomelic micromelia, relative macrocephaly with frontal bossing and midface hypoplasia, first kyphosis and than lordosis at thoracolumbal junction, trident hand with brachydactyly and limitation in elbow extension. Hypochondroplasia is allelic condition with normal face and milder skeletal involvement.

Associated major congenital anomalies

SKELETAL
- Short limbs, rhizomelia
- Long and narrow trunk
- Thoracolumbar kyphosis in infancy
- Dysplastic ilium
- Caudal narrowing of spinal canal
- Brachydactyly

Dysmorphic features/minor anomalies

- Macrocephaly with frontal bossing
- Midfacial hypoplasia with depressed nasal bridge
- Trident hand

Other

- Disproportionate short stature (short limbs)
- Hypotonia
- Obstructive sleep apnea
- Chronic otitis media
- Hyperextensible joints
- Foramen magnum cord compression
- Obesity

Genetic test

Detection of pathogenic variant in *FGFR3* gene (4p16.3). 90% of cases are de novo. More than 95% with achondroplasia have one of the two pathogenic variants G1138A and G1138C.

Name: Acrodysostosis

Synonyms:

Acrodysplasia
Arkless-Graham syndrome
Maroteaux-Malamut syndrome

ICD 10 – BPA code	Q778
ICD 9 – BPA-E*	*75658*
OMIM code	101800
ORPHA number	ORPHA950

Acrodysostosis is characterized by severe brachydactyly with relatively long first toe, peculiar round face with maxillary hypoplasia and mandibular prognathism, intellectual difficulties, notably delayed speech and impaired hearing.

Associated major congenital anomalies

SKELETAL

- Scoliosis/Kyphosis
- Spinal stenosis
- Abnormal short, malformed bones in the hands and feet
  - Brachydactyly
  - Short and broad metacarpals and phalanges
  - Cone-shaped epiphyses of the proximal and middle phalanges
  - Broad bones of the hallux
  - Spinal stenosis (75%)

Dysmorphic features/minor anomalies

- Frontal prominence
- Broad face
- Hypertelorism, epicanthus
- Maxillonasal hypoplasia
- Small hands and feet

Other

- Short stature
- Frequent otitis media
- Hearing loss
- Advanced bone age
- Obesity
- Mutiple hormonal resistence in 50%
- Developmental delay/intellectual disability (in some)

Genetic test

Detection of pathogenic variant in *PRKAR1A* gene (17q24.2) or PDE4D gene (5q11.2-q12.1)

Name: Albers-Schönberg syndrome

Synonyms:

Osteopetrosis autosomal dominant type 2
Albers-Schönberg osteopetrosis
Osteosclerosis fragilis generalisata
Marble bones, autosomal dominant

ICD 10 – BPA code	Q782
ICD 9 – BPA-E*	756540
OMIM code	166600
ORPHA number	ORPHA53

Albers-Schönberg syndrome is a form of osteopetrosis characterized by increased bone density of nearly all bones that classically displays the radiographic sign of "sandwich vertebrae" (dense bands of sclerosis parallel to the vertebral endplates).

Associated major congenital anomalies

SKELETAL

- Sclerotic and widened cranial vault
- Scoliosis
- Osteosclerosis of the spine, "sandwich vertebra" appearance
- Symmetrically increased bone density
- "Bone-within-bone" appearance primarily in the iliac wings
- Metaphyseal clubbing

Dysmorphic features/minor anomalies

Other

- Fractures
- Defects of vision and hearing, facial paresis
- Anaemia, rarely moderate bone marrow failure
- Hip osteoarthritis
- Osteomyelitis particulary affecting the mandible
- Cranial nerve compression in 5%
- Elevated serum acid phosphatase
- Reduced life span

Genetic test

Detection of pathogenic variant in *TCIRG1* gene (11q13) in 50-60%, pathogenic variant in CLCN7 gene (16p13) in 10-15%, and rarely pathogenic variant in *OSTM1* gene (6q21)

Name: Camurati-Engelmann disease

Synonyms:

Progressive diaphyseal dysplasia
Engelmann disease
Diaphyseal dysplasia 1, progressive

ICD 10 – BPA code	Q783
ICD 9 – BPA-E*	756551
OMIM code	131300
ORPHA number	ORPHA1328

Camurati-Engelmann disease is a rare craniotubular remodelling disorder characterized by hyperostosis of the long bones, skull, spine and pelvis, associated with severe pain in the extremities, a wide based waddling gait, joint contractures, muscle waisting, and easy fatigability.

Associated major congenital anomalies

SKELETAL

- Sclerosis of the basilar portions of the skull
- Scoliosis
- Contractures
- Cortical thickening of the diaphysis of the long tubular bones
- Joint contractures

Dysmorphic features/minor anomalies

- Frontal bossing
- Enlarged mandible

Other

- Sometimes marfanoid body habitus
- Eye abnormalities
- Hearing loss in less than 20%
- Increased bone density, particularly long bones
- Pain in extremities
- Decreased muscle mass and subcutaneous fat
- Muscle weakness
- Cerebellar herniation
- Hematological abnormalities
- Neurological problems (headache, vertigo, tinnitus, facial paralysis)

Genetic test

Detection of pathogenic variant in *TGFB1* gene (19q13.1) in 90% of cases

Name: **Chondrodysplasia punctata, rhisomelic, type 1**

Synonyms:

RCDP1

ICD 10 – BPA code	Q773
ICD 9 – BPA-E*	*75644*
OMIM code	215100
ORPHA number	ORPHA177

Rhizomelic chondrodysplasia punctata type 1 is a part of a group of diseases (type 1, 2, 3 and 5) in which the common characteristic is the radiographic appearance of premature small calcifications in the cartilaginous epiphyses or around the spine (stippled epiphyses). RCDP1 is the most frequent form of RCDP. Growth of the affected bones is often retarded and disturbed, which can result in rhizomelic shortening and bowing of the tubular bones, vertebral segmentation anomalies, and delayed bone maturation.

Associated major congenital anomalies

HEAD AND NECK

- Cataracts

SKELETAL

- Kyphoscoliosis
- Coronal clefts of the vertebral bodies
- Predominantly epiphyseal, frequently asymmetric calcifications at the knee, hip, elbow, shoulder
- Proximal shortening of the humerus and to a lesser degree the femur (rhizomelia)
- Flexion contractures of hips and knees

Dysmorphic features/minor anomalies

- Upward slanting palpebral fissures
- Low nasal bridge

Other

- Spasticity
- Seizures
- Sensorineural deafness
- Profound growth retardation
- Severe intellectual disability

Genetic test

Detection of pathogenic variants in the peroxisomal biogenesis factor-7 gene (PEX7) (6q23.3)

Name: Chondrodysplasia punctata 2

Synonyms:

X-linked dominant chondrodysplasia punctata
X-linked chondrodysplasia punctata type 2
Conradi-Hünermann-Happle syndrome
Chondrodystrophia calcificans congenita

ICD 10 – BPA code	Q773
ICD 9 – BPA-E*	75657
OMIM code	302960
ORPHA number	ORPHA35173

X-linked dominant chondrodysplasia punctata (type 2) is a rare genodermatosis characterized by ichthyosiform hyperkeratosis, linar or whorled atrophic and pigmentary skin lesions, chondrodysplasia punctata, asymmetric shortening of the limbs, joint contractures, cataracts and short stature.

Associated major congenital anomalies

HEAD AND NECK
- Cataract
- Microphthalmia
- Microcornea

GENITOURINARY
- Hydronephrosis

SKELETAL
- Kyphoscoliosis
- Hemivertebrae
- Asymmetric shortening of the long bones
- Rhizomelia
- Punctate calfications affecting the ends of the long bones, carpal and tarsal regions and vertebrae
- Bilateral club feet

Dysmorphic features/minor anomalies

- Frontal bossing
- Malar hypoplasia
- Flat face
- Depressed nasal bridge
- Dysplastic ears
- Short neck
- Sparse hair, eyebrows and eyelashes

Other

- Congenital ichthyosiform erythroderma in neonatal period
- Ichthyosis following Blaschko's lines in older children in 95% of cases
- Follicular atrophoderma
- Polyhydramnios
- Fetal hydrops

Genetic test

Detection of Pathogenic variant in *EBP* gene (Xp11.23-p11.22)

Name: Diastrophic dysplasia

Synonyms:

Diastrophic dwarfism

Diastrophic Nanism syndrome

ICD 10 – BPA code	Q775
ICD 9 – BPA-E*	756441
OMIM code	222600
ORPHA number	ORPHA628

Diastrophic dysplasia is marked by short stature with short extremities, multiple joint contractures, most notably of the shoulders, elbows, interphalangeal joints and hips, proximally set hypermobile thumbs (hitchhiker thumbs) and cystic masses of the external ear appearing in neonatal period.

Associated major congenital anomalies

HEAD AND NECK

- Cleft palate

SKELETAL ANOMALIES

- Scoliosis, cervical kyphosis, lumbar lordosis
- Multiple joint contractures
- Bilateral club feet
- Abducted thumbs (hitchhiker thumbs) and toes
- First metacarpal small
- Clubfoot

Dysmorphic features/minor anomalies

- Cysts on the external ear in neonatal period, later cauliflowr deformity of pinnae
- Mandibular hypoplasia
- Gap between the first and second toes

Other

- Short stature (short limbs)
- Soft cystic masses in auricle develop into hypertrophic cartilage in early infancy in 84%
- Osteoarthritis

Genetic test

Detection of pathogenic variant in *SLC26A2* gene (5q31-q34)

Name: Ellis-van-Creveld syndrome

Synonyms:

Chondroectodermal dysplasia

Mesodermic dysplasia

ICD 10 – BPA code	Q776
ICD 9 – BPA-E*	75652
OMIM code	225500; 617088
ORPHA number	ORPHA289

Ellis-van-Creveld syndrome is a skeletal and ectodermal dysplasia characterized by disproportionate short stature, postaxial polydactyly of fingers and sometimes toes, ectodermal dysplasia, and congenital heart defects.

Associated major congenital anomalies

HEAD AND NECK
- Cleft palate

CARDIOVASCULAR
- Atrial septum defect
- Single atrium
-

GENITOURINARY
- Epispadia
- Hypospadia

SKELETAL
- Narrow thorax with short ribs
- Pelvic dysplasia
- Disproportionate, irregularly short extremities especially forearm and lower leg
- Hypoplasia of upper lateral tibi
- Genu valgum
- Postaxial or axial hexadactyly with or without fusion of metacarpals and/or phalanges
- Talipes equinovarus

Dysmorphic features/minor anomalies

- Sparse, absent, or fine textured hair
- Short upper lip bound by frenula to alveolar ridge
- Small teeth, hypodontia, natal teeth
- Hypoplastic nails
- Cryptorchidism
-

Other

- Disproportionate short stature

Genetic test

Detection of pathogenic variant in *EVC1* or *EVC2* gene (both on 4p16.2 locus) in 50% of cases

Name: Enchondromatosis

Synonyms:

Dyschondroplasia
Ollier disease (Q7848)
Maffucci syndrome (with vascular anomalies) (Q7840)

ICD 10 – BPA code	Q7848/Q7840
ICD 9 – BPA-E*	756410/75642
OMIM code	166000; 614569
ORPHA number	ORPHA296; 163634

Enchondromatosis is bone dysplasia characterized by the development of multiple mainly unilateral or asymmetrically distributed enchondromas throughout the metaphyses of the long bones that grow until puberty. When associated with hemangioma, the condition is known as Maffucci syndrome.

Associated major congenital anomalies

CARDIOVASCULAR

- Haemangioma, capillar, venous and especially phlebectasia, most frequently located in the dermis and subcutaneous fat adjacent to the areas of enchondromatosis (Maffucci)

SKELETAL

- Enchondromas (in 40% are unilateral), primarly in the hands, feet and tubular long bones
- Variable early bowing of the long bones, with asymmetric retarded growth

Dysmorphic features/minor anomalies

Other

- Possibilty of thrombosis and fractures
- Possibility of other malignant tumors (chondrosarcoma, ovarian juvenile granulosa cell tumor) (15% to 25%)

Genetic test

Detection of somatic heterozygous mutations in *IDH1* or *IDH2* genes

Name: Jeune asphyxiating thoracic dystrophy

Synonyms:

Asphyxiating thoracic dystrophy of the newborn
Jeune syndrome
JATD
Short-rib thoracic dysplasia 1 with or without polydactyly

ICD 10 – BPA code	Q772
ICD 9 – BPA-E*	75640
OMIM code	208500 +several
ORPHA number	ORPHA474

Jeune syndrome is a short-rib dysplasia characterized by long and narrow thorax, short limbs and radiological skeletal abnormalities including „trident" aspect of the acetabula and metaphyseal changes.

Associated congenital anomalies

CARDIOVASCULAR

GENITOURINARY
- Cystic kidneys

SKELETAL
- Long, narrow thorax
- Short ribs
- Irregular epiphyses and metaphyses with rhizomelic shortening of limbs in 88%, and brachydactyly/micromelia in 76% of children
- Relatively short ulnae and fibulae
- Hypoplastic iliac wings in infancy
- Trident acetabular roofs
- Postaxial polydactyly

Dysmorphic features/minor anomalies

- Multiple gingival frenulae

Other

- Short stature
- Respiratory difficulties in infancy
- Growth rate may be almost normal
- Possibility of liver fibrosis or nephronophthisis and progressive renal disease
- Intelligence is normal
- Lung hypoplasia
- Hirschprung disease

Genetic test

Detection of pathogenic variant in *IFT80* (3q25.33), *DYNC2H1* (11q22.3), *WDR19* (4p14) or *TTC21B* (2q24.3) gene, several other genes are also involved

Name: Kniest dysplasia
Synonyms:
Metatropic dysplasia, type II

ICD 10 – BPA code	*Q778*
ICD 9 – BPA-E*	75658
OMIM code	156550
ORPHA number	ORPHA485

Kniest dysplasia is a severe type II collagenopathy characterized by peculiar face, short trunk with dorsal kyphosis, lumbar lordosis, and short extremities with prominent joints.

Associated major congenital anomalies

HEAD AND NECK
- Cleft palate
- Pierre-Robin sequence

SKELETAL
- Platyspondyly and other vertebral anomalies
- Short trunk
- Kyphoscoliosis
- Broad and short femoral necks
- Short tubular bones with broad metaphyses and large and deformed epiphyses
- Enlarged joints
- Clubfoot

Dysmorphic features/minor anomalies

- Round face
- Bulging eyes
- Low nasal bridge
- Midface hypoplasia
- Flat nasal root

Other

- Short stature
- Deafness
- Severe myopia
- Premature osteoarthritis
- Intelligence is usually normal

Genetic test

Detection of pathogenic variant in *COL2A1* gene (12q13.11-q13.2)

Name: Metaphyseal chondrodysplasia

Synonyms:

Metaphyseal chondrodysplasia, Murk-Jansen type

ICD 10 – BPA code	Q7781
ICD 9 – BPA-E*	75645
OMIM code	156400
ORPHA number	ORPHA33067

Jansen's metaphyseal chondrodysplasia is characterized by short limb type of short stature with other skeletal anomalies and chronic parathyroid hormone-independent hypercalcemia, hypercalciuria, and mild hypophosphatemia.

Associated major congenital anomalies

HEAD AND NECK

- Choanal stenosis/atresia
- Micrognathia

SKELETAL

- Wide cranial suttures
- Sclerosis of skull
- Bowed legs
- Enlarged joins with contracture deformities of the joints and ligamentous hyperlaxity
- Severely expanded metaphyses
- Brachydactyly
- Clubfoot

Dysmorphic features/minor anomalies

- Brachycephaly
- Broad head with prominent forehead
- Prominent eyes, hypertelorism
- Prominent upper face/cheeks
- High-arched palate
- Retrognathia
- Clubbed fingers
- Clinodactyly of the 5th fingers

Other

- Severe short stature (short limbs)
- Deafness
- Waddling gait
- Hypercalcemia, hypercalciuria, mild hypophosphatemia
- Normal to low PTH (parathyroid hormone), elevated alkaline phosphatase

Genetic test

Detection of pathogenic variant in *PTHR1* gene (3p21.31)

Name: Pyle syndrome

Synonyms:

Metaphyseal dysplasia, Pyle type

ICD 10 – BPA code	Q785
ICD 9 – BPA-E*	75655
OMIM code	265900
ORPHA number	ORPHA3005

Metaphyseal dysplasia, Pyle type is a bone dysplasia characterized by genua valga, wide clavicles, expanded trabecular metaphyses, thin cortical bone, platyspondyly, and increased susceptibility to fractures.

Associated major congenital anomalies

SKELETAL

- Minimal cranial involvement i
- Platyspondyly
- Widening of the ribs and clavicles
- Marked expansion of pubic and ischial bones
- Genu valgum
- Metaphyseal widening of the long bones (Erlenmeyer flask deformity)
- Cortical metaphyseal thinning
- Expansion of distal metacarpal and phalanges

Dysmorphic features/minor anomalies

- Mandibular prognathism

Other

- Normal to tall stature
- Fractures upon minor trauma is some patients
- Elevated osteocalcin and alkaline phosphatase

Genetic test

Detection of Pathogenic variant in *SFRP4* gene (7p14.1)

Name: Metatropic dysplasia
Synonyms:
Metatropic dwarfism

ICD 10 – BPA code	Q7780
ICD 9 – BPA-E*	756442
OMIM code	156530
ORPHA number	ORPHA2635

Metatropic dwarfism syndrome is a rare spondylometaphyseal dysplasia characterized by short limbs, enlargement and limitation fo movements in joints, and severe and progressive kyphoscoliosis

Associated major congenital anomalies

SKELETAL
- Early platyspondyly
- Odontoid hypoplasia with C1-C2 subluxation
- Rapidly progressive kyphoscoliosis during childhood
- Long coccyx
- Narrow thorax
- Severe metaphyseal enlargement and shortening of long bones
- Contractures of large joints
- Prominent joints
- Brachydactyly

Dysmorphic features/minor anomalies

- Prominent forehead
- Midface hypoplasia
- Squared-off jaw

Other

- Severe cases are lethal in utero
- Sensorineural hearing loss
- Decreased pulmonary function and myelopathy with progressive kyphoscoliosis
- Peripheral axonal neuropathy
- Intelligence is normal

Genetic test

Detection of Pathogenic variant in *TRPV4* gene (12q24.1)

Name: Multiple congenital exostoses
Synonyms:
Diaphyseal aclasia
Multiple osteochondromas
Bessel-Hagen disease
Multiple cartilaginous exostoses

ICD 10 – BPA code	Q7860
ICD 9 – BPA-E*	*75647*
OMIM code	133700; 133701; 600209
ORPHA number	ORPHA321

Multiple congenital exostosis is characterized by development of mutliple osteochondromas mostly in the metaphyses but also in the diaphyses of long bones.

Associated major congenital anomalies

Dysmorphic features/minor anomalies

Other

- Osteochondromas, mean number of locations is 15-18, especially on the long bones of extremities, predominantly around the knee
- Malignant transformation is possible in 0.5-5% of cases
- Facial bones are not affected
- Peripheral nerve compression and cervical myelopathy

Genetic test

Detection of pathogenic variant in *EXT1* or *EXT2* gene (8q24.11) found in almost 90% of cases

Name: Nail-patella syndrome

Synonyms:
Onychoosteodysplasia
Turner-Kieser syndrome

ICD 10 – BPA code	Q8722
ICD 9 – BPA-E*	75683
OMIM code	161200
ORPHA number	ORPHA2614

Nail-patella syndrome is characterised classic clinical tetrad of changes in the nails, knees, and elbows, and the presence of iliac horns.

Associated major congenital anomalies

HEAD AND NECK
- Ptosis
- Cataract
- Microcornea
- Cleft lip/palate

SKELETAL
- Hypoplastic or absent patellas
- Iliac horns
- Elbow abnormalities - limitation of extension, pronation, and supination, cubitus valgus, antecubital pterygia
- Scoliosis
- Small head of radius
- Hypoplastic scapula
- Spur in midposterior ilium

MUSCLE
- Pectoralis minor aplasia
- Biceps/triceps/quadriceps aplasia

Dysmorphic features/minor anomalies

- Nails absent, hypoplastic, or dystrophic
- Clinodactyly

Other

- Ocular involvement (glaucoma) in one third of patients
- Sensorineural hearing loss
- Nephropathy in 1/3 to 1/2 of patients
- Short stature

Genetic test

Detection of pathogenic variant in *LMX1B* gene (9q33.3)

Name: Osteogenesis imperfecta

Synonyms:

Brittle bone disease

ICD 10 – BPA code	Q7800
ICD 9 – BPA-E*	75650
OMIM code	166200; 166210; 166220; 166230; 259420; 259440; 610682; 610915; 610967; 610968; 613848; 613849; 613982; 614856; 615066; 615220; 616229; 616507
ORPHA number	ORPHA:666; 216796; 216804; 216812; 216820; 216828

Osteogenesis imperfecta (OI) is characterized by fractures with minimal or absent trauma, variable dentinogenesis imperfecta (DI), and, in adult years, hearing loss. The clinical features represent a continuum ranging from perinatal lethal form to mild predisposition to fractures, normal dentition, normal stature, and normal life span. The International Nomenclature Committee for Constitutional Disorders of the Skeleton recommended to group OI Syndrome into 5 major clinical entities: Non-deforming OI with Blue Sclerae (OI type I), Perinatally Lethal OI (Type II), Progressively Deforming OI (Type III), Common Variable OI with Normal Sclerae (OI type IV) and OI with calcification in inter-osseous membranes (OI type V).

Associated major congenital anomalies

SKELETAL

- Wormian bones
- Thin ribs
- "Codfish" vertebrae
- Protrusio acetabuli
- Thin gracile bones with fractures, bowing, "popcorn" epiphyses

Type II

- Minimal calvarial mineralization
- Platyspondyly
- Small beaded ribs
- Multiple long bone fractures at birth
- Marked deformities/angulation of long bones
- Broad long bones

Dysmorphic features/minor anomalies

- Blue/gray sclerae (type I, II and III)
- Dentinogenesis imperfecta (more severe types)

Other

- Short stature
- Progressive, post-pubertal hearing loss
- Ligamentous laxity
- Osteopenia or osteoporosis

Type II

- Premature birth
- Fetal hydrops
- Abnormal development of cerebral cortex and neuronal migration

Genetic test

Detection of pathogenic variant in *COL1A1* (17q21.33) or *COL1A2* (7q21.3) genes in autosomal dominant types, or in *CRTAP* (3p22.3), *PPIB* (15q22.31) and several other genes in autosomal recessive types.

Name: Osteopoikilosis

Synonyms:

Buschke-Ollendorff syndrome
Dermatoosteopoikilosis
Disseminated dermatofibrosis with osteopoikilosis

ICD 10 – BPA code	Q7880
ICD 9 – BPA-E*	75656
OMIM code	166700
ORPHA number	ORPHA1306

Osteopoikilosis is a sclerosing dysplasia characterized by osteopoikilosis and multiple subcutaneous nevi or nodules in the skin.

Associated major congenital anomalies

SKELETAL

- Spots of increased bone density in the epiphyseal regions of the tubular bones
- Stiff joints
- Osteosclerosis

Dysmorphic features/minor anomalies

Other

- Connective tissue nevi or nodules

Genetic test

Detection of pathogenic variant in *LEMD3* gene (12q14.3)

Name: **Spondyloepiphyseal dysplasia congenita**

Synonyms:

SEDC

Spranger-Wiedemann disease

ICD 10 – BPA code	Q777
ICD 9 – BPA-E*	75646
OMIM code	183900
ORPHA number	ORPHA94068

Spondyloepiphyseal dysplasia congenita is characterized by disproportionate short stature (short trunk type), abnormal epiphyses and flattened vertebral bodies.

Associated major congenital anomalies

HEAD AND NECK

- Cleft palate

SKELETAL

- Very short trunk and neck
- Platyspondyly
- Pectus carinatum
- Kyphosis
- Scoliosis
- Shortened limbs
- Coxa vara
- Clubfoot

Dysmorphic features/minor anomalies

- Flat facial features
- Malar hypoplasia
- Hypertelorism

Other

- Short stature (short trunk)
- Myopia/retinal detachment
- Decreased hearing
- Possible odontoid hypoplasia and cervical myelopathy
- Intelligence is usually normal

Genetic test

Detection of the pathological variant in *COL2A1* gene (12q13.11-q13.2)

Name: Spondyloepiphyseal dysplasia tarda

Synonyms:

SED tarda, X-linked

Spondyloepiphyseal dysplasia, late

ICD 10 – BPA code	Q777
ICD 9 – BPA-E*	75646
OMIM code	313400
ORPHA number	ORPHA93284

Spondyloepiphyseal dysplasia tarda is characterized by disproportionate short stature in adolescence or adulthood, associated with a short trunk and arms and barrel-shaped chest.

Associated major congenital anomalies

SKELETAL

- At puberty scoliosis, short neck, thoracic kyphosis, lumbar hyperlordosis
- Coxa vara

Dysmorphic features/minor anomalies

Other

- Normal body proportions at birth
- Progressive development of short trunk dwarfism
- Early-onset progressive osteoarthritis of the hips and knees

Genetic test

Detection of pathogenic variant in *TRAPPC2* gene (Xp22.2-p22.1)

Name: Thanatophoric dysplasia

Synonyms:

Thanatophoric dwarfism

ICD 10 – BPA code	Q771
ICD 9 – BPA-E*	756443
OMIM code	187600;187601
ORPHA number	ORPHA2655; 1860; 93274

Thanatophoric dysplasia is a severe and generally lethal skeletal dysplasia presenting in the prenatal period and characterized by micromelia, macrocephaly, narrow thorax, and distinctive facial features. It includes type 1 and type 2. Type 1 has bowed ''telephone receiver'' femurs and brachydactyly, while type 2 has straight femurs and cloverleaf skull.

Associated major congenital anomalies

SKELETAL

- Cloverleaf skull (type II)
- Lethal, micromelic dwarfism
- Small foramen magnum
- Platyspondyly
- Narrow thorax
- Small ribs
- Small iliac bones
- Marked shortnes and bowing of the long bones (type I)

Dysmorphic features/minor anomalies

- Macrocephaly
- Frontal bossing
- Small face
- Low nasal bridge

Other

- Polyhydramnios
- Characteristic morphological features are present prenatally
- Redundant skin on the arms and legs
- Temporal lobe heterotopias
- Profound developmental delay and hypotonia in survivors

Genetic test

Detection of the pathogenic variant in *FGFR3* gene (4p16.3)

Associations

Name: MURCS association

Synonyms:

Müllerian duct aplasia-renal dysplasia-cervival somite anomalies syndrome
Mayer-Rokitansky-Küster-Hauser syndrome type 2
Atypical MRKH syndrome

ICD 10 – BPA code	Q518
ICD 9 – BPA-E*	75249
OMIM code	601076
ORPHA number	ORPHA2578

MURCS association consists of a nonrandom association of Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia.

Associated major congenital anomalies

HEAD AND NECK
- Cleft lip/palate

CARDIOVASCULAR (rare)
- Valvular pulmonary stenosis
- Tetralogy of Fallot

GENITOURINARY
- Unilateral renal agenesis
- Ectopic kidney
- Renal hypoplasia
- Horseshoe kidney
- Hydronephrosis
- Bicornuate uterus, or absent/hypoplastic uterus and absent proximal part of vagina

SKELETAL
- Cervicothoracic vertebral defects (especially C5-Th1)
- Klippel-Feil anomaly
- Sprengel deformity
- Rib malformation or agenesis
- Upper limb defects (Holt Oram -like)

NEUROLOGIC
- Cerebellar cysts

Dysmorphic features/minor anomalies

- Facial asymmetry
- Micrognathia
- Short neck

Other

- Short stature
- Conductive hearing loss
- Primary amenorrhea
- Infertility

Name: Oculoauriculovertebral spectrum

Synonyms:

Goldenhar syndrome
Oculoauriculovertebral dysplasia
Expanded spectrum of hemifacial microsomia
Facioauriculovertebral sequence

ICD 10 – BPA code	Q8704
ICD 9 – BPA-E*	75606
OMIM code	164210
ORPHA number	ORPHA374

Oculoauriculovertebral spectrum is a complex developmental disorder characterised mainly by anomalies of the ear, hemifacial microsomia, epibulbar dermoids and vertebral anomalies.

Associated congenital anomalies

HEAD AND NECK

- Atresia/stenosis of external auditory canal
- Anotia, absence of auricle/accessory auricle
- Auditory canal and middle ear anomaly
- Epibulbar dermoids
- Microphthalmia
- Coloboma of eyelid, iris
- Anophthalmia
- Aniridia
- Absence of lens
- Cleft lip/palate

CARDIOVASCULAR

- Atrial septal defect
- Ventricular septal defect
- Pulmonary valvular stenosis

ABDOMINAL

- Oesophageal atresia with tracheo-oesophageal fistula

GENITOURINARY

- Renal agenesis

SKELETAL

- Hemivertebrae or hypoplasia of vertebrae, most commonly cervical
- Polydactyly

NEUROLOGIC

- Hydrocephalus
- Arnold-Chiari malformation
- Absence of corpus callosum
- Occipital encephalocele

Dysmorphic features/minor anomalies

- Microtia/misshapen/dysplastic/rudimentary ear
- Accesory preauricular tags or pits
- Hypoplasia of malar, maxillary or mandibular region
- Macrostomia
- Micrognathia, mandibular hypoplasia, and anomalies of jaw

Other

- Hemifacial microsomia, including asymmetry of face
- Conductive hearing impairment
- Normal intelligence

Name: VATER association
Synonyms:
VACTERL association

ICD 10 – BPA code	Q8726
ICD 9 – BPA-E*	759895
OMIM code	192350
ORPHA code	ORPHA887

VATER is an acronym that stands for Vertebral, Anal, Tracheal, Esophageal and Renal. VATER association defects include vertebral defects (in 70%), anal atresia (in 80%), tracheoesophageal fistula with esophageal atresia (in 70%), and renal anomalies (in 53%). VACTERL association adds cardiac defects (in 53%) and limb/radial defects (in 65%). VATER/VACTERL association is diagnosed when there are at least three of anomalies present. in the patient

Associated major congenital anomalies

CARDIOVASCULAR
- Ventricular septal defects
- Tetralogy of Fallot
- Transposition of the great arteries
- Patent ductus arteriosus

ABDOMINAL
- Tracheo-esophageal fistula with or without esophageal atresia
- Anal atresia

GENITOURINARY
- Renal agenesis
- Horseshoe kidney
- Cystic kidney
- Dysplastic kidney

SKELETAL
- Vertebral anomalies
- Thumb aplasia/hypoplasia
- Radial aplasia/hypoplasia
- Radioulnar synostosis
- Preaxial polydactyly
- Syndactyly

Dysmorphic features/minor anomalies

- Single umbilical artery
- Large fontanel

Other

- Polyhydramnios
- Failure to thrive

Genetic test

Pathogenic variant in *HOXD13* gene was found in one patient

Sequences

Name: Amniotic band sequence

Synonyms:

ADAM syndrome
Amniotic deformity-adhesion-mutilation syndrome
Streeter anomaly

ICD 10 – BPA code	Q7980
ICD 9 – BPA-E*	*75688*
OMIM code	217100
ORPHA number	ORPHA1034

Amniotic band sequence occurs in association with amniotic bands, involving the limbs, craniofacial regions, spine and trunk with very variable clinical presentations ranging from simple digital band constriction or amputation to complex developmental anomalies involving central nervous system, viscera and craniofacial regions.

Associated major congenital anomalies

HEAD AND NECK
- Encephalocele
- Facial clefts
- Orbital clefts
- Eyelid coloboma
- Cleft lip and/or palate

CARDIOVASCULAR
- Ectopia cordis

RESPIRATORY
- Abnormal lung lobation

ABDOMEN
- Abdominoschisis
- Gastroschisis
- Omphalocele

GENITOURINARY
- Bladder extrophy

SKELETAL
- Thoracoschisis
- Scoliosis
- Ring-like finger constrictions
- Finger syndactyly
- Congenital amputation of a part of limb
- Talipes equinovarus

Dysmorphic features/minor anomalies

Other

Name: Caudal regression sequence

Synonyms:

Caudal dysplasia sequence
Sacral agenesis syndrome
Sacral regression syndrome

ICD 10 – BPA code	Q8980
ICD 9 – BPA-E*	*75989*
OMIM code	600145
ORPHA number	ORPHA3027

Caudal dysplasia sequence includes aplasia or hypoplaisa of the sacrum and lower spine, but it may affect also the hindgut, the urogenital system, and the lower limbs. There is a high incidence of unilateral renal agenesis in combination with vesico-ureteric reflux. It is most likely heterogeneous with respect to its etiology and developmental pathogenesis and it is known to be associated with maternal diabetes mellitus.

Associated major congenital anomalies

HEAD AND NECK
- Cleft lip/palate

CARDIOVASCULAR
- Congenital heart anomalies

ABDOMINAL
- Imperforate anus

GENITOURINARY
- Unilateral or bilateral renal agenesis
- Renal ectopia
- Fused ureters

SKELETAL
- Hemisacrum
- Sacral agenesis
- Coccygeal defects
- Fusion of the iliac wings
- Anomalies of the lower extremities (flexion of the knees, varus position of the feet)

NEUROLOGICAL
- Anterior meningocele
- Chiari I malformation
- Holoprosencephaly

Dysmorphic features/minor anomalies

- Vesicoureteric reflux

Other

- Neurogenic bladder
- Neurological deficits in the lower extremities
- Constipation

Name: Möebius sequence

Synonyms

Congenital facial diplegia

Möebius syndrome

ICD 10 – BPA code	Q8706
ICD 9 – BPA-E*	3568
OMIM code	157900
ORPHA number	ORPHA570

Möebius sequence is congenital facial palsy characterized by mask-like facies due to bilateral or rarely unilateral facial and abducens nerves paralysis. Various other congenital anomalies can be present as well.

Associated major congenital anomalies

HEAD AND NECK

- Ptosis
- Micropthalmus
- Cleft palate with cleft uvula
- Micrognathia

SKELETAL

- Poland sequence
- Occasionally Klippel-Feil anomaly
- Limb deformities, various
- Talipes equinovarus

Dysmorphic features/minor anomalies

- Expressionless face
- Epicanthus, hypertelorism
- Protruding auricle
- Flat nasal bridge
- High-arched palate, hypodontia, tongue hypoplasia

Other

- Facial nerve palsy
- Ocular muscles palsy
- Bilateral vocal cord paralysis
- Hearing loss due to chronic otitis media
- Feeding difficulties, dysphagia
- Dysarthria
- Coordination difficulties
- Intellectual disability
- Autism

Name: Pierre Robin sequence

Synonyms:

Pierre Robin syndrome
Robin sequence

ICD 10 – BPA code	Q8708
ICD 9 – BPA-E*	75603
OMIM code	261800
ORPHA number	ORPHA718

Pierre Robin sequence is characterized by hypoplasia of the mandibule that occurs before 9 weeks in utero. It includes the triad of retrognathism, glossoptosis and a posterior median velopalatal cleft. The origin of the mandibular hypoplasia is heterogeneous but is rarely associated with an osseous defect. Most commonly antenatal orofacial hypomobility is due to functional defect in rhombencephalon.

Associated major congenital anomalies

HEAD AND NECK

- Cleft palate
- Micrognathia

Dysmorphic features/minor anomalies

- Glossoptosis

Other

- Neonatal feeding problems
- Upper airway obstruction
- Neonatal respiratory distress
- Cor pulmonale

Name: Potter sequence
Synonyms:

ICD 10 – BPA code	Q606
ICD 9 – BPA-E*	753000
OMIM code	191830
ORPHA number	ORPHA1848

Potter sequence is characterized by pulmonary hypoplasia and characteristic Potter facies due to oligohydramnios. Most commonly it is developed due to renal agenesis or hypoplasia. It can be fatal shortly after birth.

Associated major congenital anomalies

RESPIRATORY
- Lung hypoplasia

GENITOURINARY
- Renal agenesis/ hypoplasia/dysplasia
- Ureteral aplasia
- Bladder aplasia/hypoplasia

SKELETAL
- Talipes equinovarus
- Spade-like hands

Dysmorphic features/minor anomalies

- Potter facies
  - Wide-set eyes
  - Large, low-set ears
  - Flattened nose
  - Receding chin

Other

- Prenatal presentation with olihohydramnios

Genetic test

Renal hypodysplasia/aplasia-1 is caused by homozygous or compound heterozygous mutation in the *ITGA8* gene (10p13)

Name: Prune-belly sequence

Synonyms:

Abdominal muscle deficiency syndrome
Eagle-Barret syndrome
Obrinsky syndrome
Triad syndrome

ICD 10 – BPA code	Q794
ICD 9 – BPA-E*	75672
OMIM code	100100
ORPHA number	ORPHA2970

Prune-belly sequence is a rare congenital disorder that includes massively enlarged bladder (megacystis) with disorganized detrusor muscle, cryptorchidism, and thin and loose abdominal musculature. It is most commonly the consequence of urethral valve formation during the development of the prostatic urethra. Male to female ratio is 20:1.

Associated major congenital anomalies

CARDIOVASCULAR
- Congenital heart defects
- Patent ductus arteriosus

ABDOMEN
- Congenital absence/laxity of the abdominal muscles
- Imperforate anus

GENITOURINARY
- Hydronephrosis
- Hydroureter
- Posterior urethral valve

SKELETAL
- Pectus excavatum
- Pectus carinatum

Dysmorphic features/minor anomalies

- Vesicoureteral reflux
- Cryptorchidism

Other

- Distended enlarged bladder
- Wrinkled abdominal skin
- Fetal urinary tract obstruction
- Oligohydramnios

Genetic test

Detection of pathogenic variant in muscarinic cholinergic receptor-3 gene (*CHRM3*) (1q43)

Name: Sirenomelia
Synonyms:
Mermaid syndrome

ICD 10 – BPA code	Q8724
ICD 9 – BPA-E*	759844
OMIM code	600145
ORPHA number	ORPHA3169

Sirenomelia is a lethal congenital condition caused by an alteration in early vascular development. It may be considered as the severe end of spectrum of caudal regression sequence. It shares some characteristics with VATER association.

Associated major congenital anomalies

HEAD AND NECK

ABDOMINAL
- Imperforate anus

GENITOURINARY
- Renal agenesis or dysgenesis
- Absent bladder
- Urethral atresia
- Absent external genitalia

SKELETAL
- Sacral and pelvic bone anomalies
- Partial or complete fusion of the lower legs

Dysmorphic features/minor anomalies

- Potter facies
- Hypertelorism
- Epicanthal folds
- Low-set ears
- Flat nose
- Receding chin
- Aberrant abdominal umbilical artery

Other

- Olygohydramnios