Eurocat

European Surveillance of Congenital Anomalies

EUROCAT Syndrome Guide

Definition and Coding of Syndromes

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INTRODUCTION AND DEFINITIONS

This Guide is intended for use by congenital anomaly registries with a primary purpose of congenital anomaly surveillance and epidemiological research. The list of syndromes given concentrate on those which are the most commonly diagnosed in early infancy or prenatally, which are commonly associated with structural malformations and/or are found in the Q-chapter of ICD/BPA10

A **syndrome** is a recognizable pattern of anomalies which are known or thought to be causally related (Opitz, 1994). The causes may be a single gene defect, a chromosomal anomaly or an environmental teratogen. Isolated malformations may also be given a syndrome diagnosis when they have a single known cause eg. congenital rubella syndrome with only cataracts.

The EUROCAT recommended variable set allows for the coding of one syndrome and eight malformations. EUROCAT codes syndrome diagnoses as a special variable in recognition of the fact that they have a known or presumed single cause, which will often warrant their separate recognition in epidemiological analysis of patterns of risk.

The International Classification of Disease v10 (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.

It is important ALWAYS to also give a text description of the syndrome.

The Online Mendelian Inheritance in Man (OMIM) 6-digit codes (website http://www3.ncbi.nlm.nih.gov/Omim/) can be used in addition (in the "McKusick" variable). OMIM codes should never replace specific ICD10/BPA coding. It is highly recommended that all coding of syndromes should be done by a medical geneticist, especially the OMIM code as it requires more knowledge of differential diagnosis, family history and genetic analysis. In this Guide, OMIM codes that are appropriate for clinical diagnoses of the majority of cases of the specified syndrome/condition are given.

Many so-called "syndromes" are not syndromes according to current clinical genetics consenses. 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.

The recommended definition of a **sequence** (Spranger, 1982) is a "pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor." A malformation, disruption or mechanical factor may give rise to a cascade of secondary problems in subsequent morphogenesis. For example, "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 pathogenetic and not a causal concept" – there may be many initial causes for the same cascade of defects. In epidemiologic analysis relating to risk, a spina bifida with a clubfoot is the same entity as a spina bifida without a clubfoot. The name of the sequence should NOT be coded in the syndrome variable, but in the first malformation variable. A list of sequences is given in Part 2 of the coding list (conditions NOT to be coded as syndromes).

An **Association** is defined by Opitz (1994) as idiopathic (ie. cause unknown) pattern of multiple anomalies arising during blastogenesis. For practical purposes, there are only three well known associations, given in Part 1 of 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 given in Part 1 only so that they can be easily distinguished and separated from syndromes and ALWAYS give the name in text. Registries should only code an association if the baby has been seen by a clinician who has named the association. There is no utility in a registry coding an association on the basis of the presence in registry records of a certain combination of anomalies or anomaly codes, 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 single known aetiology. They will usually be grouped with multiple malformations, not syndromes.

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.

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 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

as excluding such cases. Minor anomalies should also be coded and given in text, since these can be important for differential diagnosis.

Skeletal Dysplasias and other Disorders of Skeletal Development

Disorders of skeletal development can be defined as follows:

- **dysostoses** – malformations of single bones, alone or in combination
- **disruptions** – secondary malformations of bones
- **skeletal dysplasias** – developmental disorders of chondro-osseous tissue

Dysostoses are malformations, 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, Grieg acrocephalopolysyndatcyly etc).
Disruptions arise due to toxic and other unfavourable exposures of the embryo. They produce secondary malformations (example -thalidomide tetraphocomelia, amniotic bands).
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).

Skeletal dysplasias are not always defined as syndromes, but are considered equivalent to syndromes for EUROCAT purposes because they have a single known genetic origin. Many of them are known under their eponyms as syndromes (e.g. Jeune´s syndrome, Maffucci syndrome, Ellis van Creveld syndrome etc). They are listed separately in this guide to help them to be found for coding. Some of the conditions that are now in the syndrome list in this guide but not listed under skeletal dysplasias will eventually pass into the skeletal dysplasias group as our knowledge of their biological basis progresses (e.g. Leri-Weill or Robinow syndrome).
See also further coding notes no. 13.

References.

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.

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.

Further Coding Notes and Explanation of Guide.

1. The first coding column gives the ICD10-BPA codes. ICD10-BPA is available on the EUROCAT Membership Only 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" and special care should be given to the text description.

2. The second coding column gives the usual OMIM code, where the condition has Mendelian inheritance.

3. The third 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.

4. 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.

5. Part 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 explanation given in text descriptions.

7. In case of both a diagnosed syndrome and a microdeletion, code both the syndrome (see syndrome list) and give the code for the microdeletion (Q936). Give the microdeletion description in the karyotype text and the syndrome name

in the syndrome text. The distinction between deletions and microdeletions is becoming less clear as new techniques are used. Moreover, more microdeletions are being discovered as the genetic basis for syndromes. At the time of writing the most common syndromes with a microdeletion are Di George (microdeletion 22q11), Prader Willi (15q11, pat), Angelman (15q11, mat), Williams (7q11), Miller Dieker (17p13), Alagille (20p12), Smith Magenis (17p11), WAGR -Aniridia Wilms (11p13), TAR (1p21), Rubinstein Taybi (16p13), Sotos (5q35), 1p36 deletion . The last of these has no syndrome name, and this may become more common as new microdeletions are discovered where a syndrome had not previously been recognized - code as a microdeletion (Q936) and be sure to give the description in text (both in karyotype and syndrome name text).

8. The new technologies such as array-CGH mean that small deletions and duplications are being found that were not envisaged in ICD10 under Q93.5 (other deletions of part of a chromosome) and Q92.3 (minor partial trisomy). At the moment we continue to use those codes, but it is sensible to record as much information as possible in text regarding the nature of the deletion, and how it was discovered, and later coding revisions will consider this issue further. If you know that the deletion is a microdeletion, code under Q93.6 as in coding note 7.

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

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

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

12. For congenital infections (eg. Rubella, CMV) and other exogenous syndromes (eg. valproate) include only syndromes due to early pregnancy exposure with major malformations. Code all component malformation

13. SKELETAL DYSPLASIA. If a final diagnosis of a lethal or severe skeletal dysplasia is not possible, as in TOP 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

Part 1
Conditions to be Coded In The "Syndrome" Field

Description	ICD10-BPA*	OMIM code	ICD9-BPA-E*
Syndromes – monogenic or unknown etiology			
Aarskog syndrome	Q8710	305400, 100050	*75989*
Acrocephalopolysyndactyly (all types)	Q8700	201000 ;101600 ;201020;101120	755501
Aglosso-adactyly	*Q878*	103300	759846
Alagille syndrome	Q4471	118450	*75167*
Alport's syndrome	Q8780	104200,203780,301050	759870
Angelman syndrome	Q8785	105830	759899
Aniridia- Wilms tumour syndrome WAGR	Q13.1	194072	
Apert's syndrome (acrocephalosyndactyly type I and II)	Q8701	101200	755500/01
Bardet-Biedl syndrome	Q8781	209900	759820
Beckwith-Wiedemann syndrome (EMG syndrome)	Q8730	130650	759874
Blepharophimosis-ptosis syndrome	*Q100*	110100	*74360*
CHARGE	*Q300*		
Cleidocranial dysplasia (dysostosis)	Q7402	119600	755551
Cockayne's syndrome	Q8711	216400	759826
Cornelia de Lange syndrome (de Lange syndrome)	Q8712	122470	759821
Crouzons disease (craniofacial dysostosis type I)	Q751	123500	75601
Di George syndrome/velocardiofacial syndrome	D821	188400	27910
Dubowitz syndrome	Q8713	223370	*75989*
Ehlers-Danlos syndrome	Q796	130000 + several	75685
Fragile X syndrome	Q992	309550	*75888*
Frasers syndrome (cryptophthalmos-syndactyly)	*Q8702*[1]	219000	759892
Frontonasal dysplasia	Q7581	136760	
Gardner syndrome	Q8583	175100	759630
Gorlin-Chaudhry-Moss syndrome	*Q878*	233500	759898
Hallermann-Streiff syndrome	Q8705	234100	756050
Holt-Oram syndrome (heart-hand syndrome)	Q8720	142900	759842
Incontinentia pigmenti	Q823	308300	75735

* Codes printed in italics are not specific to the syndrome listed [1] Note that WHO use the unspecified code Q112

Description	ICD10-BPA*	OMIM code	ICD9-BPA-E*
Ivemark syndrome	*Q206*	208530	*75989*
Jervell-Lange-Nielsen syndrome	*Q878*	220400	42680
Kartagener's syndrome	Q8934	244400	759340
Kaufman-McKusick syndrome	*Q518*	236700	*75248*
Klippel-Feil syndrome	Q761	148900	756110
Klippel-Trenaunay (-Weber) syndrome (angioosteohypertrophy)	Q8721	149000	759840
Larsen's syndrome	Q7484	150250; 245600	75581
Laurence-Moon syndrome	Q8781	245800	759822
Lenz microphthalmos syndrome	*Q112*	309800	
Leprechaunism	*Q878*	246200	25982
Leri-Weill syndrome (dyschondrosteosis)	*Q871B*	127300	756581
Marchesani (-Weill) syndrome	*Q875*	277600	759897
Marfan's syndrome	*Q874*	154700	759860
Marinesco-Sjögren syndrome	*Q878*	248800	33430
McCune-Albright syndrome (polyostotic fibrous dysplasia)	Q781	174800	756512
Meckel Gruber	Q6190	249000	*75989*
Melnick-Fraser syndrome (brankio-oto-renal)	*Q178*	113650	*75989*
Miller-Dieker	Q04.3	247200	
Noonan's syndrome	Q8714	163950	759896
Oculomandibular dysostosis	Q755		
Oro-facial-digital syndrome (all types inc.Papillon-Leage, Psaume, Mohr etc)	Q8707	311200; 252100; 277170	759802
Otopalatodigital syndrome (all types)	*Q870F*	311300; 304120	759845
Pena-Shokeir syndrome (fetal akinesia)	Q870E	208150	*75989*
Peutz-Jeghers syndrome	Q8580	175200	759600
Pfeiffer syndrome, Noack syndrome, acrocephalosyndactyly type V	*Q750*	101600	755501
Poland's syndrome	Q7982	173800	75680
Popliteal pterygium syndrome	*Q798*	119500: 263650	756885
Prader-Willi syndrome	Q8715	176270	759872
Robinow-Silverman-Smith syndrome	Q8716	180700, 268310	*75989*
Rothmund-Thomson syndrome	*Q828*	268400	757303

* Codes printed in italics are not specific to the syndrome listed.

Description	ICD10-BPA*	OMIM code	ICD9-BPA-E*
Rubinstein-Taybi syndrome	Q8723	180849	759841
Russell-Silver syndrome	Q8717	312780	759823
Schwartz-Jampel syndrome (chondrodystrophic myotonia)	G7116	255800	*75688*
Seckel's syndrome	Q8718	210600	759827
Silver's syndrome	Q8717	180860	759823
Sjögren-Larsson syndrome	Q871A	270200	75712
Smith-Lemli-Opitz syndrome	Q8719	270400	759828
Smith-Magenis	Q87.8	182290	
Sotos syndrome	Q8731	117550	756883
Stickler syndrome	Q8709	108300, 604841, 184840	*75989*
Sturge-Weber syndrome	Q8581	185300	759611
TAR syndrome	Q8725	274000	*75526*
Treacher-Collins syndrome (mandibulofacial dysostosis)	Q754[1]	154500	756041
Tricho-rhino-phalangeal syndrome	*Q870B*	190350	*75989*
Ullrich-Feichtiger's syndrome (dyscraniopygophalangism)	Q870D	no OMIM	759890
Van der Woude syndrome	*Q380*	119300	*75989*
Velocardiofacial syndrome/DiGeorge syndrome	D821	188400	27910
Von Hippel Lindau syndrome	Q8582	193300	101.....
Waardenburg's syndrome	E7030	193500	759804
Weaver syndrome	Q8732	277590	*75989*
Whistling face syndrome (Freeman-Sheldon syndrome)	Q870C	193700	759807
Williams syndrome	Q8784	194050	*75989*
Zellweger's disease or syndrome	Q8783	214100	759875
Teratogenic syndromes			
Fetal Alcohol syndrome	Q860		76076
Fetal Cytomegalovinis (CMV) syndrome	P351		7711
Fetal Hydantoin syndrome	Q861		
Fetal Rubella syndrome	P350		7710 or 7602
Fetal Thalidomide syndrome	Q8682		

* Codes printed in italics are not specific to the syndrome listed. [1]There are 2 codes for this syndrome. Q754 is recommended by WHO

Description	ICD10-BPA*	OMIM code	ICD9-BPA-E*
Fetal Toxoplasmosis	P371		77121
Fetal Valproate syndrome	Q8680		
Fetal Warfarin syndrome	Q862		
Skeletal dysplasias *(see also coding note 13)*			
Achondrogenesis	Q770		
Achondrogenesis type I	Q7700	200600, 600972	
Achondrogenesis type II	Q7701	200610	
Achondroplasia/hypochondroplasia	Q774	100800	75643
Acrodysostosis	*Q778*	101800	
Albers-Schonberg syndrome (osteopetrosis)	Q782	166600	756540
Camurati-Engelmann disease (diaphyseal dysplasia)	Q783	131300	756551
Chondrodysplasia punctata (Conradi-Hunermann etc)	*Q773*	118650; 302960	*75657*
Diastrophic dysplasia	Q775	222600	756441
Ellis-van Creveld syndrome (chondroectodermal dysplasia)	Q776	225500	75652
Enchondromatosis	Q784	166000	
Hypochondrogenesis	Q7702		
Jeune's syndrome (asphyxiating thoracic dysplasia, short rib syndrome)	Q772	208500	75640
Kniest dysplasia	*Q778*	156550	
Maffucci syndrome (osteochondromatosis with haemangiomata)	Q7840	166000	756421
Metaphyseal chondrodysplasia	*Q7781*	156400	
Metaphyseal dysplasia, Pyle's syndrome	Q785	123000	
Metatropic dwarfism	Q7780	250600	756442
Multiple congenital exostosis, diaphyseal aclasia	Q786	133700	
Nail patella syndrome (onycho-osteodysplasia)	Q8722	161200	75683
Osteochondromatosis syndrome, Dyschondroplasia, Ollier	Q7848		756410
Osteogenesis imperfecta Type II (neonatal lethal form)	Q7800	166210	*75650*
Osteopoikilosis	Q7880	166700	
Spondyloepiphyseal dysplasia	Q777	183900, 313400	
Thanatophoric dysplasia	Q771	187600; 151210	756443

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

Description	ICD10-BPA*	OMIM code	ICD9-BPA-E*
Microdeletions *(see coding note 7)*			
Specified microdeletion	Q936		
Chromosomal syndromes			
Pallister-Killian (tetrasomy 12p)	Q922		
Cri du chat syndrome (5p deletion)	Q934		758311
Down's (trisomy 21)	Q900-Q909		75800
Edward's (trisomy 18)	Q910-Q913		75820
Klinefelter (47,XXY)	Q980		75870
Patau's syndrome (trisomy 13)	Q914-Q917		75810
Turner (45,X, monosomy X)	Q960-Q969		75860
Wolff-Hirschorn syndrome (4p deletion)	Q933		75832
Associations			
Goldenhar's syndrome (oculoauriculovertebral dysplasia)	Q8704		75606
MURCS syndrome/association	*Q518*		
VATER association	Q8726		759895

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

Part 2

Conditions Which Should NOT Be Coded As Syndromes (Code as malformation instead)

Description	ICD10-BPA*	OMIM code	ICD9-BPA-E*
Sequences			
Amniotic band sequence	Q7980		
Caudal dysplasia sequence	Q8980		
Moebius sequence	Q8706		3568
Pierre Robin sequence	Q8708		75603
Potter's sequence	Q606		753000
Prune-belly sequence	Q794		75672
Sirenomelia	Q8724		759844
Malformations with syndrome names but not a syndrome			
Apple peel syndrome	Q411		
Arnold-Chiari syndrome	Q070		
Arthrogryposis multiplex congenita	Q743		
Congenital blind loop syndrome	Q438		
Conjoined twins	Q894		
Constriction ring syndrome of upper limb NOS	Q719		
Constriction ring syndrome of lower limb NOS	Q729		
Cryptophthalmos syndrome	Q8702		
Cyclops syndrome	Q8703		
Dandy-Walker syndrome/malformation	Q031		
Eisenmenger syndrome	Q2181		
Herlitz syndrome (epidermolysis bullosa)	Q811		
Hirschprung syndrome/disease	Q431		
Hypoplastic left heart syndrome	Q234		
Hypoplastic right heart syndrome	Q226		
Lutembacher's syndrome (ASD+mitral stenosis)	Q2114		
Marcus Gunn's syndrome/phenomenon	Q0780		

Megacystis-megaureter syndrome/sequence	Q6476		
Pharyngeal pouch syndrome	D821		
Scimitar syndrome	Q268		
Siemen's syndrome	Q828		
Small left colon syndrome	Q432		
Taussig-Bing syndrome	Q201		

* Codes printed in italics are not specific to the syndrome/malformation listed