NIFTY® mono

200+ Monogenic Diseases

Gene-Disease List

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This document is displayed in alphabetical order of diseases.

This document combines and displays the same disease subtypes described in the OMIM database.

The disease descriptions in this document are mainly from the [Description] in the OMIM database, and may differ from the report descriptions.

This document is only provided for users to understand the disease. Please refer to the report for clinical consultation.

Please note do not share to another non-relevant person.

1. Achondrogenesis, type II or hypochondrogenesis; ACG2 (OMIM 200610)

COL2A1 gene (OMIM 120140) on chromosome 12q13; AD

Achondrogenesis type II (ACG2) is characterized by severe micromelic dwarfism with small chest and prominent abdomen, incomplete ossification of the vertebral bodies, and disorganization of the costochondral junction. ACG2 is an autosomal dominant trait occurring mostly as new mutations. However, somatic and germline mosaicism have been reported.

2. Achondroplasia; ACH (OMIM 100800)

FGFR3 gene (OMIM 134934) on chromosome 4p16.3; AD

Achondroplasia (ACH) is the most frequent form of short-limb dwarfism. Affected individuals exhibit short stature caused by rhizomelic shortening of the limbs, characteristic facies with frontal bossing and midface hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, and trident hand.

3. Acrodysostosis 1, with or without hormone resistance; ACRDYS1 (OMIM 101800)

PRKAR1A gene (OMIM 188830) on chromosome 17q24; AD

Acrodysostosis-1 (ACRDYS1) is a form of skeletal dysplasia characterized by short stature, severe brachydactyly, facial dysostosis, and nasal hypoplasia. Affected individuals often have advanced bone age and obesity. Laboratory studies show resistance to multiple hormones, including parathyroid, thyrotropin, calcitonin, growth hormone-releasing hormone, and gonadotropin. However, not all patients show endocrine abnormalities.

4. Alagille syndrome; ALGS

Alagille syndrome (ALGS) is a complex multisystem disorder involving primarily the liver, heart, eyes, face, and skeleton. The clinical features are highly variable, even within families. The major clinical manifestations of ALGS are cholestasis, characterized by bile duct paucity on liver biopsy; congenital cardiac defects, primarily involving the pulmonary arteries; posterior embryotoxin in the eye; typical facial features; and butterfly vertebrae. Renal and central nervous abnormalities also occur. Mortality is approximately 10%, with vascular accidents, cardiac disease, and liver disease accounting for most of the deaths.

4.1 Alagille syndrome 1; ALGS1 (OMIM 118450)

JAG1 gene (OMIM 601920) on chromosome 20p12; AD

A form of Alagille syndrome.

4.2 Alagille syndrome 2; ALGS2 (OMIM 610205)

NOTCH2 gene (OMIM 600275) on chromosome 1p12; AD

A form of Alagille syndrome.

5. Alexander disease; ALXDRD (OMIM 203450)

GFAP gene (OMIM 137780) on chromosome 17q21; AD

In decreasing order of frequency, 3 forms of Alexander disease (ALXDRD) are recognized, based on age of onset: infantile, juvenile, and adult. Younger patients typically present with seizures, megalencephaly, developmental delay, and spasticity. In older patients, bulbar or pseudobulbar symptoms predominate, frequently accompanied by spasticity. The disease is progressive, with most patients dying within 10 years of onset. Imaging studies of the brain typically show cerebral white matter abnormalities, preferentially affecting the frontal region. All 3 forms have been shown to be caused by mutations in the GFAP gene.

6. Alternating hemiplegia of childhood 1; AHC1 (OMIM 104290)

ATP1A2 gene (OMIM 182340) on chromosome 1q23; AD

Alternating hemiplegia of childhood 1 (AHC1) is a rare syndrome of episodic hemi- or quadriplegia lasting minutes to days. Most cases are accompanied by dystonic posturing, choreoathetoid movements,

nystagmus, other ocular motor abnormalities, autonomic disturbances, and progressive cognitive impairment.

7. Andersen syndrome (OMIM 170390)

KCNJ2 gene (OMIM 600681) on chromosome 17q24; AD

Andersen cardiodysrhythmic periodic paralysis, also known as Andersen syndrome or Andersen-Tawil syndrome, is an autosomal dominant multisystem channelopathy characterized by periodic paralysis, ventricular arrhythmias, and distinctive dysmorphic facial or skeletal features. Hypoplastic kidney and valvular heart disease have also been reported. The disorder shows marked intrafamilial variability and incomplete penetrance.

8. Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis; ABS2 (OMIM 207410)

FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

The Antley-Bixler syndrome (ABS) is an exceptionally rare craniosynostosis syndrome characterized by radiohumeral synostosis present from the perinatal period. There is a wide spectrum of anomalies seen in ABS, including midface hypoplasia, choanal stenosis or atresia, and multiple joint contractures. Mortality has been reported to be as high as 80% in the neonatal period, primarily due to airway compromise, and prognosis improves with increasing age.

9. Apert syndrome (OMIM 101200)

FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

Apert syndrome is a congenital disorder characterized primarily by craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet with a tendency to fusion of bony structures. Most cases are sporadic, but autosomal dominant inheritance has been reported.

10. Atelosteogenesis; AO

Atelosteogenesis is a lethal chondrodysplasia characterized by distal hypoplasia of the humeri and femurs, hypoplasia of the midthoracic spine, occasionally complete lack of ossification of single hand bones, and the finding in cartilage of multiple degenerated chondrocytes encapsulated in fibrous tissue.

10.1 Atelosteogenesis, type I; AO1 (OMIM 108720)

FLNB gene (OMIM 603381) on chromosome 3p14; AD

A form of Atelosteogenesis.

10.2 Atelosteogenesis, type III; AO3 (OMIM 108721)

FLNB gene (OMIM 603381) on chromosome 3p14; AD

A form of Atelosteogenesis.

11. Au-Kline syndrome; AUKS (OMIM 616580)

HNRNPK gene (OMIM 600712) on chromosome 9q21; AD

Au-Kline syndrome (AUKS) is an autosomal dominant disorder characterized by hypotonia, global developmental delay, characteristic facies (long palpebral fissures, shallow orbits, ptosis, a broad nasal bridge, hypoplastic alae nasi, downturned corners of the mouth and a long face), congenital heart defects, genitourinary abnormalities, skeletal abnormalities, and variable other congenital malformations.

12. Coffin-Siris syndrome; CSS

Coffin-Siris syndrome is a multiple malformation syndrome characterized by mental retardation associated with coarse facial features, hypertrichosis, sparse scalp hair, and hypoplastic or absent fifth fingernails or toenails. Other more variable features may include poor overall growth, craniofacial abnormalities, spinal anomalies, and congenital heart defects.

12.1 Coffin-Siris syndrome 1; CSS1 (OMIM 135900)

ARID1B gene (OMIM 614556) on chromosome 6q25; AD

A form of Coffin-Siris syndrome.

12.2 Coffin-Siris syndrome 2 / MENTAL RETARDATION, AUTOSOMAL DOMINANT 14; CSS2 (OMIM 614607)

ARID1A gene (OMIM 603024) on chromosome 1p36; AD

A form of Coffin-Siris syndrome.

12.3 Coffin-Siris syndrome 3 / MENTAL RETARDATION, AUTOSOMAL DOMINANT 15; CSS3 (OMIM 614608)

SMARCB1 gene (OMIM 601607) on chromosome 22q11; AD

A form of Coffin-Siris syndrome.

12.4 Coffin-Siris syndrome 4 / MENTAL RETARDATION, AUTOSOMAL DOMINANT 16; CSS4 (OMIM 614609)

SMARCA4 gene (OMIM 603254) on chromosome 19p13; AD

A form of Coffin-Siris syndrome.

12.5 Coffin-Siris syndrome 5; CSS5 (OMIM 616938)

SMARCE1 gene (OMIM 603111) on chromosome 17q21; AD

A form of Coffin-Siris syndrome.

13. Helsmoortel-van der Aa syndrome / MENTAL RETARDATION, AUTOSOMAL DOMINANT 28; HVDAS (OMIM 615873)

ADNP gene (OMIM 611386) on chromosome 20q13; AD

Helsmoortel-Van der Aa syndrome (HVDAS) is a neurodevelopmental disorder characterized by impaired intellectual development/motor delay, autism spectrum disorder, facial dysmorphisms, hypotonia, congenital heart disease, visual difficulties, and gastrointestinal issues.

14. Bainbridge-Ropers syndrome; BRPS (OMIM 615485)

ASXL3 gene (OMIM 615115) on chromosome 18q12; AD

Bainbridge-Ropers syndrome (BRPS) is a developmental disorder characterized by delayed psychomotor development, severe intellectual disability with poor or absent speech, hypotonia, feeding difficulties, poor growth, and dysmorphic facial features.

15. Baraitser-Winter syndrome; BRWS

Baraitser-Winter syndrome (BRWS) is a rare developmental phenotype characterized by the combination of hypertelorism, broad nose with large tip and prominent root, congenital nonmyopathic ptosis, ridged metopic suture, arched eyebrows, iris or retinal coloboma, sensorineural deafness, shoulder girdle muscle bulk and progressive joint stiffness, and pachygyria with anteroposterior severity gradient, rarely lissencephaly or neuronal heterotopia. Cleft lip and palate, hallux duplex, congenital heart defects and renal tract anomalies are seen in some cases. Microcephaly may develop with time. Early muscular involvement, occasionally with congenital arthrogryposis, may be present. Intellectual disability and epilepsy are variable in severity and largely correlate with central nervous system anomalies.

15.1 Baraitser-Winter syndrome 1; BRWS1 (OMIM 243310)

ACTB gene (OMIM 102630) on chromosome 7p22; AD

A form of Baraitser-Winter syndrome.

15.2 Baraitser-Winter syndrome 2; BRWS2 (OMIM 614583)

ACTG1 gene (OMIM 102560) on chromosome 17q25; AD

A form of Baraitser-Winter syndrome.

16. Beare-Stevenson cutis gyrata syndrome; BSTVS (OMIM 123790)

FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

Beare-Stevenson cutis gyrata syndrome (BSTVS) is an autosomal dominant condition characterized by the furrowed skin disorder of cutis gyrata, acanthosis nigricans, craniosynostosis, craniofacial dysmorphism, digital anomalies, umbilical and anogenital abnormalities, and early death.

17. Bent bone dysplasia syndrome; BBDS1 (OMIM 614592)

FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

Bent bone dysplasia syndrome-1 (BBDS1) is a perinatal lethal skeletal dysplasia characterized by poor mineralization of the calvarium, craniosynostosis, dysmorphic facial features, prenatal teeth, hypoplastic pubis and clavicles, osteopenia, and bent long bones.

18. Blepharophimosis-impaired intellectual development syndrome; BIS (OMIM 619293)

SMARCA2 gene (OMIM 600014) on chromosome 9p24; AD

Blepharophimosis-impaired intellectual development syndrome (BIS) is a congenital disorder characterized by a distinct facial appearance with blepharophimosis and global development delay. Affected individuals have delayed motor skills, sometimes with inability to walk, and impaired intellectual development with poor or absent speech; some patients show behavioral abnormalities. There are recognizable facial features, including epicanthal folds, sparse eyebrows, broad nasal bridge, short nose with downturned tip, and open mouth with thin upper lip. Other more variable features include distal skeletal anomalies, feeding difficulties with poor growth, respiratory infections, and hypotonia with peripheral spasticity.

19. Bohring-Opitz syndrome; BOPS (OMIM 605039)

ASXL1 gene (OMIM 612990) on chromosome 20q11; AD

Bohring-Opitz syndrome (BOPS) is a malformation syndrome characterized by severe intrauterine growth retardation, poor feeding, profound mental retardation, trigonocephaly, prominent metopic suture, exophthalmos, nevus flammeus of the face, upslanting palpebral fissures, hirsutism, and flexion of the elbows and wrists with deviation of the wrists and metacarpophalangeal joints.

20. Boomerang dysplasia; BOOMD (OMIM 112310)

FLNB gene (OMIM 603381) on chromosome 3p14; AD

Boomerang dysplasia (BOOMD) is a perinatal lethal osteochondrodysplasia characterized by absence or underossification of the limb bones and vertebrae.

21. Bosch-Boonstra-Schaaf optic atrophy syndrome; BBSOAS (OMIM 615722)

NR2F1 gene (OMIM 132890) on chromosome 5q15; AD

Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS) is an autosomal dominant disorder characterized by delayed development, moderately impaired intellectual development, and optic atrophy. Most patients also have evidence of cerebral visual impairment. Dysmorphic facial features are variable and nonspecific.

22. Campomelic dysplasia; CMPD (OMIM 114290)

SOX9 gene (OMIM 608160) on chromosome 17q24; AD

Campomelic dysplasia (CMPD) is an autosomal dominant skeletal dysplasia characterized by congenital shortness and bowing of long tubular bones, especially in the lower extremities, as well as by hypoplastic

scapulae, narrow iliac wings, and nonmineralized thoracic pedicles. CMPD is often lethal in the first year of life, due to respiratory insufficiency related to small chest size and tracheobronchial hypoplasia.

23. Cardiac, facial, and digital anomalies with developmental delay; CAFDADD (OMIM 618164)

TRAF7 gene (OMIM 606692) on chromosome 16p13; AD

Cardiac, facial, and digital anomalies with developmental delay (CAFDADD) is a multisystemic developmental disorder with variable cardiac and digital anomalies and facial dysmorphism. Some patients may have seizures and ocular/aural abnormalities.

24. Cardiofaciocutaneous syndrome; CFC

Cardiofaciocutaneous (CFC) syndrome is a multiple congenital anomaly disorder characterized by a distinctive facial appearance, heart defects, and mental retardation. The heart defects include pulmonic stenosis, atrial septal defect, and hypertrophic cardiomyopathy. Some patients have ectodermal abnormalities such as sparse and friable hair, hyperkeratotic skin lesions, and a generalized ichthyosis-like condition. Typical facial characteristics include high forehead with bitemporal constriction, hypoplastic supraorbital ridges, downslanting palpebral fissures, a depressed nasal bridge, and posteriorly angulated ears with prominent helices.

24.1 Cardiofaciocutaneous syndrome; CFC1 (OMIM 115150)

BRAF gene (OMIM 164757) on chromosome 7q34; AD

A form of Cardiofaciocutaneous syndrome.

24.2 Cardiofaciocutaneous syndrome 2; CFC2 (OMIM 615278)

KRAS gene (OMIM 190070) on chromosome 12p12; AD

A form of Cardiofaciocutaneous syndrome.

24.3 Cardiofaciocutaneous syndrome 3; CFC3 (OMIM 615279)

MAP2K1 gene OMIM 176872) on chromosome 15q22; AD

A form of Cardiofaciocutaneous syndrome.

24.4 Cardiofaciocutaneous syndrome 4; CFC4 (OMIM 615280)

MAPK2K2 gene (OMIM 601263) on chromosome 19p13; AD

A form of Cardiofaciocutaneous syndrome.

25. Cerebellar dysfunction with variable cognitive and behavioral abnormalities; CECBA (OMIM 614756)

CAMTA1 gene (OMIM 611501) on chromosome 1p36; AD

Cerebellar dysfunction with variable cognitive and behavioral abnormalities (CECBA) is an autosomal dominant neurologic disorder with significant phenotypic heterogeneity, even within families. The disorder is most often diagnosed through genetic analysis with retrospective clinical phenotyping. Symptom onset is usually in early childhood, although later onset, even in adulthood, has been reported. Most affected individuals show global developmental delay from early childhood, particularly of motor and language skills. Many have mild intellectual disability; behavioral and psychiatric abnormalities such as autism and obsessive-compulsive disorder are also often observed. The movement disorder is prominent and may include cerebellar signs such as ataxia, tremor, dysmetria, poor coordination, and dysarthria. Other abnormal movements including spasticity, myoclonus, and dystonia have been reported, thus widening the phenotypic spectrum. Brain imaging is usually normal, but may show cerebellar atrophy or nonspecific white matter lesions. Variable dysmorphic facial features may also be present.

26. CHARGE syndrome (OMIM 214800)

CHD7 gene (OMIM 608892) on chromosome 8q12; AD

CHARGE syndrome is characterized by a pattern of congenital anomalies including choanal atresia and malformations of the heart, inner ear, and retina.

27. CHILD syndrome (OMIM 308050)

NSDHL gene (OMIM 300275) on chromosome Xq28; XLD

CHILD syndrome is an acronym for an X-linked dominant disorder characterized by congenital hemidysplasia with ichthyosiform erythroderma and limb defects. The mutations are lethal in hemizygous males.

28. Chitayat syndrome; CHYTS (OMIM 617180)

ERF gene (OMIM 611888) on chromosome 19q13; AD

Chitayat syndrome (CHYTS) is a rare condition characterized by respiratory distress presenting at birth, bilateral accessory phalanx resulting in shortened index fingers with ulnar deviation, hallux valgus, and characteristic facial features including prominent eyes, hypertelorism, depressed nasal bridge, full lips, and upturned nose.

29. Chondrodysplasia punctata, X-linked dominant; CDPX2 (OMIM 302960)

EBP gene (OMIM 300205) on chromosome Xp11; XLD

Chondrodysplasia punctata (CDP) is a clinically and genetically heterogeneous disorder characterized by punctiform calcification of the bones. X-linked dominant CDP, also known as Conradi-Hunermann syndrome, is the most well-characterized form. CDPX2 arises almost exclusively in females and is usually lethal in males. In addition to radiographic stippling, the disorder is characterized by rhizomelic shortness, transient congenital ichthyosis following the lines of Blaschko, patchy alopecia, cataracts, and midface hypoplasia. Affected males are extremely rare and the clinical features in males almost always result from postzygotic mosaicism for an EBP mutation.

30. Cleidocranial dysplasia (OMIM 119600)

RUNX2 gene (OMIM 600211) on chromosome 6p21; AD

The main clinical features of cleidocranial dysplasia (CLCD) include persistently open skull sutures with bulging calvaria, hypoplasia or aplasia of the clavicles permitting abnormal facility in apposing the shoulders, wide pubic symphysis, short middle phalanx of the fifth fingers, dental anomalies, and often vertebral malformation.

31. Coffin-Lowry syndrome; CLS (OMIM 303600)

RPS6KA3 gene (OMIM 300075) on chromosome Xp22; XLD

Coffin-Lowry syndrome is a rare form of X-linked mental retardation characterized by skeletal malformations, growth retardation, hearing deficit, paroxysmal movement disorders, and cognitive impairment in affected males and some carrier females.

32. Cognitive impairment with or without cerebellar ataxia; CIAT (OMIM 614306)

SCN8A gene (OMIM 600702) on chromosome 12q13; AD

Cognitive impairment with or without cerebellar ataxia (CIAT) is a disorder characterized by markedly delayed cognitive and motor development, attention deficit disorder, and cerebellar ataxia. Features include bilateral esophoria, strabismatic amblyopia, unsustained gaze evoked nystagmus on horizontal gaze, ataxic gait, dysmetria in the upper limbs and dysarthria, with normal strength, tone, and reflexes. The disease is caused by mutations affecting the gene represented in this entry.

33. Congenital contractures of the limbs and face, hypotonia, and developmental delay; CLIFAHDD (OMIM 616266)

NALCN gene (OMIM 611549) on chromosome 13q33; AD

Congenital contractures of the limbs and face, hypotonia, and developmental delay (CLIFAHDD) is a congenital disorder characterized by congenital contractures of the limbs and face, resulting in characteristic facial features, hypotonia, and variable degrees of developmental delay. All reported cases have occurred de novo.

34. Cornelia de Lange syndrome; CDLS

The Cornelia de Lange syndrome (CDLS) is a multisystem malformation syndrome recognized primarily on the basis of characteristic facial dysmorphism, including low anterior hairline, arched eyebrows, synophrys, anteverted nares, maxillary prognathism, long philtrum, thin lips, and 'carp' mouth, in association with prenatal and postnatal growth retardation, mental retardation and, in many cases, upper limb anomalies. However, there is wide clinical variability in this disorder, with milder phenotypes that may be difficult to ascertain on the basis of physical features.

34.1 Cornelia de Lange syndrome 1; CDLS1 (OMIM 122470)

NIPBL gene (OMIM 608667) on chromosome 5p13; AD

A form of Cornelia de Lange syndrome.

34.2 Cornelia de Lange syndrome 2; CDLS2 (OMIM 300590)

SMC1A gene (OMIM 300040) on chromosome Xp11; XLD

A form of Cornelia de Lange syndrome.

34.3 Cornelia de Lange syndrome 3; CDLS3 (OMIM 610759)

SMC3 gene (OMIM 606062) on chromosome 10q25; AD

A form of Cornelia de Lange syndrome.

34.4 Cornelia de Lange syndrome 4; CDLS4 (OMIM 614701)

RAD21 gene (OMIM 606462) on chromosome 8q24; AD

A form of Cornelia de Lange syndrome.

34.5 Cornelia de Lange syndrome 5; CDLS5 (OMIM 300882)

HDAC8 gene (OMIM 300269) on chromosome Xq13; XLD

A form of Cornelia de Lange syndrome.

35. Cortical dysplasia, complex, with other brain malformations; CECBM

Complex cortical dysplasia with other brain malformations (CDCBM) is a disorder of aberrant neuronal migration and disturbed axonal guidance. Affected individuals have mild to severe mental retardation, strabismus, axial hypotonia, and spasticity. Brain imaging shows variable malformations of cortical development, including polymicrogyria, gyral disorganization, and fusion of the basal ganglia, as well as thin corpus callosum, hypoplastic brainstem, and dysplastic cerebellar vermis. Extraocular muscles are not involved.

35.1 Cortical dysplasia, complex, with other brain malformations 5; CDCBM5 (OMIM 615763)

TUBB2A gene (OMIM 615101) on chromosome 6p25; AD

A form of Complex cortical dysplasia with other brain malformations.

35.2 Cortical dysplasia, complex, with other brain malformations 6; CDCBM6 (OMIM 615763)

TUBB gene (OMIM 191130) on chromosome 6p21; AD

A form of Complex cortical dysplasia with other brain malformations.

36. Costello syndrome; CSTLO (OMIM 218040)

HRAS gene (OMIM 190020) on chromosome 11p15; AD

Costello syndrome is a rare multiple congenital anomaly syndrome associated in all cases with characteristic coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, and failure to thrive. Other features include cardiac anomalies and developmental disability. Facial warts, particularly nasolabial, are often present in childhood.

37. Craniofrontonasal dysplasia; CFNS (OMIM 304110)

EFNB1 gene (OMIM 300035) on chromosome Xq13; XLD

Craniofrontonasal syndrome is an X-linked developmental disorder that shows paradoxically greater severity in heterozygous females than in hemizygous males. Females have frontonasal dysplasia, craniofacial asymmetry, craniosynostosis, bifid nasal tip, grooved nails, wiry hair, and abnormalities of the thoracic skeleton, whereas males typically show only hypertelorism.

38. Craniosynostosis; CRS

Craniosynostosis is a primary abnormality of skull growth involving premature fusion of the cranial sutures such that the growth velocity of the skull often cannot match that of the developing brain. This produces skull deformity and, in some cases, raises intracranial pressure, which must be treated promptly to avoid permanent neurodevelopmental disability.

38.1 Craniosynostosis 1; CRS1 (OMIM 123100)

TWIST1 gene (OMIM 601622) on chromosome 7p21; AD

A form of Craniosynostosis.

38.2 Craniosynostosis 2; CRS2 (OMIM 604757)

MSX2 gene (OMIM 123101) on chromosome 5q35; AD

A form of Craniosynostosis.

38.3 Craniosynostosis 4; CRS4 (OMIM 600775)

ERF gene (OMIM 611888) on chromosome 19q13; AD

A form of Craniosynostosis.

39. Crouzon syndrome (OMIM 123500)

FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

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

40. Crouzon syndrome with acanthosis nigricans, CAN (OMIM 612247)

FGFR3 gene (OMIM 134934) on chromosome 4p16; AD

Crouzon syndrome with acanthosis nigricans (CAN), also called Crouzonodermoskeletal syndrome, is a disorder characterized by craniosynostosis during development and a skin condition called acanthosis nigricans. The signs and symptoms overlap with those of a similar condition called Crouzon syndrome. Common features include wide-set, bulging eyes, strabismus; a beaked nose; and an underdeveloped upper jaw. Patients are usually of normal intelligence. Acanthosis nigricans is the feature different from Crouzon syndrome. In addition, subtle changes may be seen in the bones of the spine (vertebrae) on X-rays. Noncancerous growths called cementomas may develop in the jaw during young adulthood.

41. Developmental and epileptic encephalopathy 2; DEE2 (OMIM 300672)

CDKL5 gene (OMIM 300203) on chromosome Xp22; XLD

Developmental and epileptic encephalopathy-2 (DEE2) is an X-linked dominant severe neurologic disorder characterized by onset of seizures in the first months of life and severe global developmental delay resulting in impaired intellectual development and poor motor control. Other features include lack of speech development, subtle dysmorphic facial features, sleep disturbances, gastrointestinal problems, and stereotypic hand movements.

42. Developmental and epileptic encephalopathy 4; DEE4 (OMIM 612164)

STXBP1 gene (OMIM 602926) on chromosome 9q34; AD

Developmental and epileptic encephalopathy-4 (DEE4) is a neurologic disorder characterized by the onset of tonic seizures in early infancy (usually in first months of life). In most cases, seizures increase in frequency and become refractory. Affected individuals have profoundly impaired psychomotor development with poor head control, limited or no ability to walk, spastic quadriplegia, and poor or absent speech. Brain imaging may show cortical atrophy and hypomyelination. EEG studies in the more severe cases show a burst-suppression pattern, consistent with a clinical diagnosis of Ohtahara syndrome, and/or hypsarrhythmia, consistent with a clinical diagnosis of West syndrome. Less severely affected individuals have later onset of seizures.

43. Developmental and epileptic encephalopathy 5; DEE5 (OMIM 613477)

SPTAN1 gene (OMIM 182810) on chromosome 9q34; AD

Developmental and epileptic encephalopathy-5 (DEE5) is a neurologic disorder characterized by global developmental delay and the onset of tonic seizures or infantile spasms in the first months of life. The seizures tend to be refractory to treatment, and EEG shows hypsarrhythmia, consistent with a clinical diagnosis of West syndrome. Affected individuals have severely impaired psychomotor development with lack of visual attention, poor head control, feeding difficulties, microcephaly, and spastic quadriplegia. Brain imaging may show cerebral atrophy and hypomyelination.

44. Early Infantile Epileptic Encephalopathy 6 / Dravet syndrome; DEE6A (OMIM 607208)

SCN1A gene (OMIM 182389) on chromosome 2q24; AD

Early Infantile Epileptic Encephalopathy 6 (DEE6A) is a clinical term for a severe neurologic disorder characterized by the onset of seizures in the first year of life after normal early development. Affected individuals usually present with generalized tonic, clonic, and tonic-clonic seizures that may initially be induced by fever and are usually refractory to treatment. Later, patients tend to manifest other seizure types, including absence, myoclonic, and partial seizures. The EEG is often normal at first, but later characteristically shows generalized spike-wave activity and other abnormalities. Psychomotor development stagnates around the second year of life, and affected individuals show subsequent mental decline, behavioral problems, and learning disabilities. 'Severe myoclonic epilepsy of infancy' (SMEI) and 'migrating partial seizures of infancy' (MPSI) are other clinical manifestations of Dravet syndrome.

45. Developmental and epileptic encephalopathy 6B, non-Dravet; DEE6B (OMIM 619317)

SCN1A gene (OMIM 182389) on chromosome 2q24; AD

Developmental and epileptic encephalopathy-6B (DEE6B) is a severe neurodevelopmental disorder characterized by early-infantile seizure onset, profoundly impaired intellectual development, and a hyperkinetic movement disorder. Brain imaging usually shows progressive atrophy and other abnormalities.

46. Developmental and epileptic encephalopathy 7; DEE7 (OMIM 613720)

KCNQ2 gene (OMIM 602235) on chromosome 20q13; AD

Developmental and epileptic encephalopathy-7 (DEE7) is a neurologic disorder characterized by the onset of refractory seizures in early infancy, often in the neonatal period. Affected individuals have resultant delayed neurologic development and persistent neurologic abnormalities. EEG initially shows a burst suppression pattern, consistent with a clinical diagnosis of Ohtahara syndrome, which may later evolve to multifocal epileptiform activity. Brain imaging in some patients shows lesions in the basal ganglia. Seizures usually remit by age 3 or 4 years, with improvement of EEG abnormalities and possibly brain imaging abnormalities, but the severe neurologic deficits persist.

47. Developmental and epileptic encephalopathy 11; DEE11 (OMIM 613721)

SCN2A gene (182390) on chromosome 2q24; AD

Developmental and epileptic encephalopathy-11 (DEE11) is a neurologic disorder characterized by onset of seizures in the first days, weeks, or months of life. Some patients may have later onset. Seizures comprise multiple types, including tonic, generalized, and myoclonic, and tend to be refractory to medication. However, some patients with onset of seizures before 3 months of age may respond to sodium channel blockers, particularly phenytoin. About half of patients become seizure-free in childhood. Affected individuals have global developmental delay, usually with severely impaired intellectual development, although some may be less severely affected and show autism spectrum disorder. Additional common features include microcephaly, hypotonia, and abnormal movements, such as dystonia, dyskinesias, and choreoathetotic movements. Brain imaging may show white matter defects. The phenotype is highly variable, even in patients with the same mutation.

48. Developmental and epileptic encephalopathy 13; DEE13 (OMIM 614558)

SCN8A gene (600702) on chromosome 12q13; AD

Developmental and epileptic encephalopathy-13 (DEE13) is a neurologic disorder characterized by the onset of intractable seizures in the first year of life. Some patients may present with seizures in the first days, whereas others present later (between 2 and 7 months of age) after normal or only mild developmental delay. Affected individuals have profoundly impaired development or developmental regression after the onset of seizures, and show severe intellectual disability, poor or absent language, hypotonia, and are usually unable to walk. EEG shows variable abnormalities, including multifocal and generalized spike-wave discharges, sometimes with status epilepticus or hypsarrhythmia. Brain imaging may show cerebral atrophy.

49. Developmental and epileptic encephalopathy 14; DEE14 (OMIM 614959)

KCNT1 gene (608167) on chromosome 9q34; AD

Developmental and epileptic encephalopathy-14 (DEE14) is a severe neurologic disorder characterized by onset in the first 6 months of life of refractory focal seizures and arrest of psychomotor development. Ictal EEG shows discharges that arise randomly from various areas of both hemispheres and migrate from one brain region to another. The disorder presents as 'malignant migrating partial seizures of infancy' (MMPSI), a clinical designation.

50. Developmental and epileptic encephalopathy 17; DEE17 (OMIM 615473)

GNAO1 gene (139311) on chromosome 16q13; AD

Developmental and epileptic encephalopathy-17 (DEE17) is a severe neurologic disorder characterized by onset of intractable seizures in the first weeks or months of life. EEG often shows a burst-suppression pattern consistent with a clinical diagnosis of Ohtahara syndrome. Affected infants have very poor psychomotor development and may have brain abnormalities, such as cerebral atrophy or thin corpus callosum. Some patients may show involuntary movements.

51. Developmental and epileptic encephalopathy 19; DEE19 (OMIM 615744)

GABRA1 gene (OMIM 137160) on chromosome 5q34; AD

Developmental and epileptic encephalopathy-19 (DEE19) is a neurologic disorder characterized by the onset of various types of seizures in the first year of life, usually between 8 and 12 months of age. Seizures are often triggered by fever, and status epilepticus may occur. Affected individuals subsequently show mildly to moderately impaired intellectual development. Brain imaging is typically normal. The clinical phenotype is similar to that of Dravet syndrome.

52. Developmental and epileptic encephalopathy 26; DEE26 (OMIM 616056)

KCNB1 gene (OMIM 600397) on chromosome 20q13; AD

Developmental and epileptic encephalopathy-26 (DEE26) is a neurologic disorder characterized by onset of variable types of seizures late in infancy or in the first years of life. Affected children show developmental delay with intellectual disability, poor speech, and behavioral abnormalities. EEG shows multifocal epileptic discharges, and may show hypsarrhythmia.

53. Developmental and epileptic encephalopathy 27; DEE27 (OMIM 616139)

GRIN2B gene (OMIM 138252) on chromosome 12p12; AD

Developmental and epileptic encephalopathy-27 (DEE27) is an autosomal dominant neurodevelopmental disorder characterized by delayed psychomotor development and intellectual disability of variable severity associated with early-onset seizures. Additional features may include hypotonia, abnormal movements, such as dystonia, and autistic features. Some patients may have structural malformations of cortical development on brain imaging. The phenotype is highly variable and reflects a spectrum of neurodevelopmental abnormalities that range from mild intellectual disability without seizures to an encephalopathy.

54. Developmental and epileptic encephalopathy 31A; DEE31A (OMIM 616346)

DNM1 gene (OMIM 602377) on chromosome 9q34; AD

Developmental and epileptic encephalopathy-31A (DEE31A) is an autosomal dominant neurologic disorder characterized by the global developmental delay apparent in early infancy. Most individuals have onset of various types of refractory seizures in the first months or years of life, which exacerbates the psychomotor deficits. Patients have hypotonia and profound intellectual disability with absent speech and inability to walk or ataxic gait. Some patients may have additional features, including dysmorphic features or cortical visual impairment.

55. Developmental and epileptic encephalopathy 42; DEE42 (OMIM 617106)

CACNA1A gene (OMIM 601011) on chromosome 19p13; AD

Developmental and epileptic encephalopathy-42 (DEE42) is a neurologic disorder characterized by the onset of various types of seizures in the first hours or days of life, although rare patients may have onset in the first weeks of life. The seizures tend to be refractory and associated with EEG abnormalities, including multifocal spikes and generalized spike-wave complexes. Affected infants show global developmental delay with severely impaired intellectual development. Other features may include axial hypotonia, peripheral hypertonia with hyperreflexia, tremor, ataxia, and abnormal eye movements.

56. Developmental and epileptic encephalopathy 54; DEE54 (OMIM 617391)

HNRNPU gene (OMIM 602869) on chromosome 1q44; AD

Developmental and epileptic encephalopathy-54 (DEE54) is a severe neurodevelopmental disorder characterized by delayed psychomotor development, early-onset refractory seizures that are often initially febrile but later afebrile, and severe intellectual disability.

57. Developmental and epileptic encephalopathy 92; DEE92 (OMIM 617829)

GABRB2 gene (OMIM 600232) on chromosome 5q34; AD

Developmental and epileptic encephalopathy-92 (DEE92) is characterized in most patients by onset of seizures in infancy or childhood and associated with global developmental delay and variable impairment of intellectual development. The seizure type and severity varies, and seizures may be intractable in some patients. Some patients are severely affected, unable to walk or speak, whereas others show some development. Additional neurologic features, including cortical blindness, dystonia, and spasticity, may occur.

58. Developmental and epileptic encephalopathy 94; DEE94 (OMIM 615369)

CHD2 gene (OMIM 602119) on chromosome 15q26; AD

Developmental and epileptic encephalopathy-94 (DEE94) is a severe form of epilepsy characterized by onset of multiple seizure types in the first few years of life and associated with poor prognosis. Affected individuals have cognitive regression and impaired intellectual development.

59. Developmental and epileptic encephalopathy 98; DEE98 (OMIM 619605)

ATP1A2 gene (OMIM 182340) on chromosome 1q23; AD

Developmental and epileptic encephalopathy-98 (DEE98) is characterized by onset of seizures in the first decade (range infancy to late childhood) associated with variable global developmental delay. Other features may include hypotonia, spasticity, and quadriparesis. Brain imaging may be normal or show nonspecific and variable abnormalities, including polymicrogyria. The severity is variable; some patients may die of refractory status epilepticus.

60. Developmental and epileptic encephalopathy 99; DEE99 (OMIM 619606)

ATP1A3 gene (OMIM 182350) on chromosome 19q13; AD

Developmental and epileptic encephalopathy-99 (DEE99) is characterized by onset of seizures in early childhood associated with global developmental delay and severely impaired intellectual development. Other features may include hypotonia, quadriparesis, nystagmus, and apnea. Brain imaging may be normal or show nonspecific and variable abnormalities, including cerebral atrophy and polymicrogyria. The severity is variable; some patients die of refractory status epilepticus.

61. Developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities; DEHMBA (OMIM 619595)

SRCAP gene (611421) on chromosome 16p11; AD

Developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities (DEHMBA) is an early-onset neurodevelopmental disorder characterized by these features. Affected individuals also have nonspecific and variable dysmorphic facial features that do not constitute a recognizable gestalt. Although the disorder is caused by truncating mutations in the SRCAP gene as is FLHS, the DEHMBA phenotype is clinically distinguishable from FLHS by the lack of short stature, brachydactyly, and delayed bone age, as well as absence of a specific facial appearance. There are some overlapping features between the 2 disorders, mainly impaired intellectual development and speech delay.

62. Dias-Logan syndrome (OMIM 617101)

BCL11A gene (606557) on chromosome 2p16.

Intellectual developmental disorder with persistence of fetal hemoglobin (Dias-Logan syndrome) is characterized by delayed psychomotor development, intellectual disability, variable dysmorphic features, including microcephaly, downslanting palpebral fissures, strabismus, and external ear abnormalities, and asymptomatic persistence of fetal hemoglobin (HbF).

63. Epiphyseal dysplasia, multiple, 1; EDM1 (OMIM 132400)

COMP gene (OMIM 600310) on chromosome 19p13; AD

Multiple epiphyseal dysplasia is a skeletal disorder characterized by short stature and early-onset osteoarthrosis.

64. Epiphyseal dysplasia, multiple, 2; EDM2 (OMIM 600204)

COL9A2 gene (OMIM 120260) on chromosome 1p34; AD

Multiple epiphyseal dysplasia is a clinically and genetically heterogeneous skeletal disorder characterized by joint pain and stiffness, mild short stature, and degenerative joint disease. Onset of the disorder is usually in childhood.

65. Epiphyseal dysplasia, multiple, 3, with or without myopathy; EDM3 (OMIM 600969)

COL9A3 gene (OMIM 120270) on chromosome 20q13; AD

Multiple epiphyseal dysplasia is characterized by early-onset short stature, waddling gait, and stiffness and/or pain in the knees and sometimes other joints.

66. Episodic ataxia, type 9; EA9 (OMIM 618924)

SCN2A gene (OMIM 182390) on chromosome 2q23; AD

Episodic ataxia type 9 (EA9) is a neurologic disorder characterized by onset of ataxic episodes in the first years of life. Features may include difficulty walking, dizziness, slurred speech, headache, vomiting, and pain. The ataxic episodes vary in frequency and duration; most tend to occur every few weeks or months and last minutes to hours. Prior to the EA, most patients have neonatal- or infantile-onset tonic or generalized tonic-clonic (GTC) seizures that may be severe and refractory to medication, but remit later in infancy or early childhood, either spontaneously or concurrently with medication. Some patients have mildly delayed development with speech delay and/or autistic features or mildly impaired intellectual development. However, others show normal psychomotor development. Treatment of the ataxic episodes with acetazolamide is effective in about 50% of patients.

67. Fibrodysplasia ossificans progressiva; FOP (OMIM 135100)

ACVR1 gene (OMIM 102576) on chromosome 2q24; AD

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disease with complete penetrance involving progressive ossification of skeletal muscle, fascia, tendons, and ligaments. FOP has a prevalence of approximately 1 in 2 million worldwide, and shows no geographic, ethnic, racial, or gender preference. Individuals with FOP appear normal at birth except for great toe abnormalities: the great toes are short, deviated, and monophalangic. Ossification occurs progressively over the course of a lifetime in an inevitable and unpredictable episodic manner, with most patients being confined to a wheelchair by the third decade of life and requiring lifelong care.

68. Floating-Harbor syndrome; FLHS/FHS (OMIM 136140)

SRCAP gene (OMIM 611421) on chromosome 16p11; AD

Floating-Harbor syndrome (FLHS) is a rare genetic disorder characterized by proportionate short stature, delayed bone age, delayed speech development, and typical facial features. The face is triangular with deep-set eyes, long eyelashes, bulbous nose, wide columella, short philtrum, and thin lips.

69. Fontaine progeroid syndrome; FPS (OMIM 612289)

SLC25A24 gene (OMIM 608744) on chromosome 1p36; AD

Fontaine progeroid syndrome (FPS) is characterized by prenatal and postnatal growth retardation, decreased subcutaneous fat tissue, sparse hair, triangular face, widely open anterior fontanel, convex and broad nasal ridge, micrognathia, craniosynostosis in some patients, and early death in many.

70. GAND syndrome; GAND (OMIM 615074)

GATAD2B gene (OMIM 614998) on chromosome 1q21; AD

GAND syndrome is a neurodevelopmental syndrome characterized by global developmental delay apparent from infancy, with motor delay and moderate to severely impaired intellectual development. Most patients have poor speech acquisition, especially expressive language development, and may manifest signs of speech apraxia. Affected individuals have hypotonia and feeding difficulties in infancy, as well as common dysmorphic features, such as macrocephaly, frontal bossing, hypertelorism, deep-set eyes, posteriorly rotated ears, and elongated wide nose with prominent nasal tip. More variable features may include seizures, cardiac abnormalities, and nonspecific findings on brain imaging.

71. Genitopatellar syndrome; GTPTS (OMIM 606170)

KAT6B gene (OMIM 605880) on chromosome 10q22; AD

Genitopatellar syndrome is a rare disorder consisting of microcephaly, severe psychomotor retardation, and characteristic coarse facial features, including broad nose and small or retracted chin, associated with congenital flexion contractures of the lower extremities, abnormal or missing patellae, and urogenital anomalies.

72. Glass syndrome; GLASS (OMIM 612313)

SATB2 gene (608148) on chromosome 2q33; AD

Glass syndrome (GLASS) is characterized by intellectual disability of variable severity and dysmorphic facial features, including micrognathia, downslanting palpebral fissures, cleft palate, and crowded teeth. Additional features may include seizures, joint laxity, arachnodactyly, and happy demeanor.

73. Hajdu-Cheney syndrome; HJCYS (OMIM 102500)

NOTCH2 gene (600275) on chromosome 1p12; AD

Hajdu-Cheney syndrome (HJCYS) is a rare autosomal dominant skeletal disorder characterized by short stature, coarse and dysmorphic facies, bowing of the long bones, and vertebral anomalies. Facial features include hypertelorism, bushy eyebrows, micrognathia, small mouth with dental anomalies, low-set ears, and short neck. There is progressive focal bone destruction, including acroosteolysis and generalized osteoporosis. Additional and variable features include hearing loss, renal cysts, and cardiovascular anomalies.

74. Holt-Oram syndrome; HOS (OMIM 142900)

TBX5 gene (OMIM 601620) on chromosome 12q24; AD

Holt-Oram syndrome is an autosomal dominant disorder characterized by abnormalities of the upper limbs and shoulder girdle, associated with a congenital heart lesion. The typical combination is considered to be a triphalangeal thumb with a secundum atrial septal defect (ASD), but there is a great range in the severity of both the heart and skeletal lesions.

75. Hutchinson-Gilford progeria syndrome; HGPS (OMIM 176670)

LMNA (OMIM 150330) on chromosome 1q22; AD

Hutchinson-Gilford progeria syndrome is a rare disorder characterized by short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, and facial features that resemble aged persons. Cardiovascular compromise leads to early death. Cognitive development is normal. Onset is usually within the first year of life.

76. Hyper-IgE recurrent infection syndrome / Hyper-IgE syndrome-1 with recurrent infections; HIES1 (OMIM 147060)

STAT3 gene (OMIM 102582) on chromosome 17q21; AD

Hyper-IgE syndrome-1 with recurrent infections (HIES1) is an autosomal dominant immunologic disorder characterized by chronic eczema (atopy), recurrent Staphylococcal infections, increased serum IgE, and eosinophilia. Other more variable immunologic abnormalities include defective granulocyte chemotaxis, abnormalities in T-lymphocyte subgroups, impaired antibody production, and decreased production of or response to certain cytokines. Importantly, the same immune system defects are not found in all patients. Some patients may have a distinctive coarse facial appearance, abnormal dentition, hyperextensibility of the joints, and bone fractures.

77. Hypochondroplasia; HCH (OMIM 146000)

FGFR3 gene (OMIM 134934) on chromosome 4p16; AD

Hypochondroplasia (HCH) is an autosomal dominant disorder characterized by short-limbed dwarfism, lumbar lordosis, short and broad bones, and caudad narrowing of the interpediculate distance of the lumbar spine. It shows some resemblance to achondroplasia, but is much milder and can be distinguished on clinical and radiographic grounds.

78. Impaired intellectual development and distinctive facial features with or without cardiac defects; MRFACD (OMIM 616789)

MED13L gene (OMIM 608771) on chromosome 12q24; AD

Impaired intellectual development and distinctive facial features with or without cardiac defects (MRFACD) is an autosomal dominant, complex syndromic neurodevelopmental disorder characterized by delayed psychomotor development, poor speech acquisition, distinctive dysmorphic facial features, including frontal bossing, upslanting palpebral fissures, depressed nasal bridge with bulbous tip, and macrostomia. There is variable penetrance of cardiac malformations, ranging from no malformations to patent foramen ovale to septal defects and/or transposition of the great arteries.

79. Intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia; MICPCH (OMIM 300749)

CASK gene (OMIM 300172) on chromosome Xp11; XLD

Intellectual developmental disorder with microcephaly and pontine and cerebellar hypoplasia (MICPCH) is an X-linked disorder affecting males and females. In females, it is characterized by severely impaired intellectual development and variable degrees of pontocerebellar hypoplasia. Affected females have poor psychomotor development, often without independent ambulation or speech, and axial hypotonia with or without hypertonia. Some may have sensorineural hearing loss, eye anomalies, or seizures. Dysmorphic features include overall poor growth, severe microcephaly (-3.5 to -10 SD), broad nasal bridge and tip, large ears, long philtrum, micrognathia, and hypertelorism. Like females with MICPCH, affected males have microcephaly that is congenital or evolves rapidly during the first few months of life. MRI findings show significant or severe pontocerebellar hypoplasia. MICPCH in males may occur with or without severe epileptic encephalopathy in addition to severe to profound developmental delay. When seizures are present, they occur early and may be intractable. A few males have been noted to have MICPCH and severe developmental delay but without severe epilepsy.

80. Intellectual developmental disorder with autism and macrocephaly; IDDAM (OMIM 615032)

CHD8 gene (OMIM 610528) on chromosome 14q11; AD

Intellectual developmental disorder with autism and macrocephaly (IDDAM) is characterized by impaired intellectual development, a highly penetrant autism spectrum phenotype, and macrocephaly. Other common features include tall stature, gastrointestinal symptoms, distinct facial features, sleep problems, and attention problems.

81. Intellectual developmental disorder with language impairment with or without autistic features (OMIM 613670)

FOXP1 gene (OMIM 605515) on chromosome 3p13; AD

Intellectual developmental disorder with language impairment and with or without autistic features is a neurodevelopmental disorder characterized by global developmental delay with moderate to severe speech delay that particularly affects expressive speech. Most patients have articulation defects, but frank verbal dyspraxia is not observed. Common dysmorphic features include broad forehead, downslanting palpebral fissures, short nose with broad tip, relative macrocephaly, frontal hair upsweep, and prominent digit pads. Gross motor skills are also delayed. Some patients have autistic features and/or behavioral problems. All reported cases have occurred *de novo*.

82. Intellectual developmental disorder, autosomal dominant; MRD

Intellectual developmental disorder, autosomal dominant (MRD) is an autosomal dominant neurodevelopmental disorder characterized by delayed psychomotor development and intellectual disability of variable severity.

82.1 Intellectual developmental disorder, autosomal dominant 5; MRD5 (OMIM 612621)

SYNGAP1 gene (OMIM 603384) on chromosome 6p21; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.2 Intellectual developmental disorder, autosomal dominant 6, with or without seizures; MRD6 (OMIM 613970)

GRIN2B gene (OMIM 138252) on chromosome 12p13; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.3 Intellectual developmental disorder, autosomal dominant 7; MRD7 (OMIM 614104)

DYRK1A gene (OMIM 600855) on chromosome 21q22; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.4 Intellectual developmental disorder, autosomal dominant 13; MRD13 (OMIM 614563)

DYNC1H1 gene (OMIM 600112) on chromosome 14q32; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.5 Intellectual developmental disorder, autosomal dominant 21; MRD21 (OMIM 615502)

CTCF gene (OMIM 604167) on chromosome 16q22; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.6 Intellectual developmental disorder, autosomal dominant 23; MRD23 (OMIM 615761)

SETD5 gene (OMIM 615743) on chromosome 3p25; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.7 Intellectual developmental disorder, autosomal dominant 29; MRD29 (OMIM 616078)

SETBP1 gene (OMIM 611060) on chromosome 18q12; AD

A form of Intellectual developmental disorder, autosomal dominant.

82.8 Intellectual developmental disorder, autosomal dominant 41; MRD41 (OMIM 616944)

TBL1XR1 gene (OMIM 608628) on chromosome 3q26; AD

A form of Intellectual developmental disorder, autosomal dominant.

83. Houge-Janssens syndrome; HJS

Houge-Janssens syndrome (HJS) is characterized by global developmental delay, hypotonia, variably impaired intellectual development, poor speech, and dysmorphic facial features. Additional more variable features may include macrocephaly and seizures.

83.1 Houge-Janssens syndrome 1 / Intellectual developmental disorder, autosomal dominant 35; HJS1/MRD35 (OMIM 616355)

PPP2R5D gene (OMIM 601646) on chromosome 6p21; AD

A form of Houge-Janssens syndrome.

83.2 Houge-Janssens syndrome 2 / Intellectual developmental disorder, autosomal dominant 36; HJS2/MRD36 (OMIM 616362)

PPP2R1A gene (OMIM 605983) on chromosome 19q13; AD

A form of Houge-Janssens syndrome.

84. Jackson-Weiss syndrome; JWS (OMIM 123150)

FGFR2 gene (OMIM 176943) on chromosome 10q26 / FGFR1 gene (OMIM 136350) on chromosome 8p11; AD

Jackson-Weiss syndrome (JWS) is an autosomal dominant condition consisting of craniosynostosis characterized by premature fusion of the cranial sutures as well as radiographic anomalies of the feet.

85. Kabuki syndrome 1; KABUK1 (OMIM 147920)

KMT2D gene (OMIM 602113) on chromosome 12q13; AD

Kabuki syndrome is a congenital mental retardation syndrome with additional features, including postnatal dwarfism, a peculiar facies characterized by long palpebral fissures with eversion of the lateral third of the lower eyelids (reminiscent of the make-up of actors of Kabuki, a Japanese traditional theatrical form), a broad and depressed nasal tip, large prominent earlobes, a cleft or high-arched palate, scoliosis, short fifth finger, persistence of fingerpads, radiographic abnormalities of the vertebrae, hands, and hip joints, and recurrent otitis media in infancy.

86. KBG syndrome; KBGS (OMIM 148050)

ANKRD11 gene (OMIM 611192) on chromosome 16q24; AD

KBG syndrome (KBGS) is characterized by macrodontia of the upper central incisors, distinctive craniofacial findings, short stature, skeletal anomalies, and neurologic involvement that includes global developmental delay, seizures, and intellectual disability.

87. Kleefstra syndrome 1; KLEFS1 (OMIM 610253)

EHMT1 gene (OMIM 607001) on chromosome 9q34; AD

Kleefstra syndrome 1 is characterized by severe mental retardation, hypotonia, brachy(micro)cephaly, epileptic seizures, flat face with hypertelorism, synophrys, anteverted nares, everted lower lip, carp mouth with macroglossia, and heart defects.

88. Koolen-De Vries syndrome; KDVS (OMIM 610443)

KANSL1 gene (OMIM 612452) on chromosome 17q21; AD

Koolen-De Vries syndrome (KDVS) is characterized by moderately to severely impaired intellectual development, hypotonia, friendly demeanor, and highly distinctive facial features, including tall, broad forehead, long face, upslanting palpebral fissures, epicanthal folds, tubular nose with bulbous nasal tip, and large ears. More variable features include cardiac or genitourinary anomalies and seizures.

89. Larsen Syndrome; LRS (OMIM 150250)

FLNB gene (OMIM 603381) on chromosome 3p14; AD

Larsen syndrome is an osteochondrodysplasia characterized by large-joint dislocations and characteristic craniofacial abnormalities. The cardinal features of the condition are dislocations of the hip, knee and elbow joints, with equinovarus or equinovalgus foot deformities. Spatula-shaped fingers, most marked in the thumb, are also present. Craniofacial anomalies include hypertelorism, prominence of the forehead, a depressed nasal bridge, and a flattened midface. Cleft palate and short stature are often associated features. Spinal anomalies include scoliosis and cervical kyphosis. Hearing loss is a well-recognized complication.

90. LEOPARD syndrome 3; LPRD3 (OMIM 613707)

BRAF gene (OMIM 164757) on chromosome 7q34; AD

LEOPARD syndrome is characterized by multiple freckles, electrocardiographic conduction abnormalities, hypertelorism, pulmonary stenosis, genital anomalies, growth retardation, and sensorineural hearing loss.

91. Leukodystrophy, hypomyelinating, 6; HLD6 (OMIM 612438)

TUBB4A gene (OMIM 602662) on chromosome 19p13; AD

Hypomyelinating leukodystrophy-6, also known as hypomyelinating leukodystrophy with atrophy of the basal ganglia and cerebellum, is a neurologic disorder characterized by onset in infancy or early childhood of delayed motor development and gait instability, followed by extrapyramidal movement disorders, such as dystonia, choreoathetosis, rigidity, opisthotonus, and oculogyric crises, progressive spastic tetraplegia, ataxia, and, more rarely, seizures. Most patients have cognitive decline and speech delay, but some can function normally. Brain MRI shows a combination of hypomyelination, cerebellar atrophy, and atrophy or disappearance of the putamen.

92. Lissencephaly 3; LIS3 (OMIM 611603)

TUBA1A gene (OMIM 602529) on chromosome 12q13; AD

Lissencephaly (LIS) is characterized by smooth or nearly smooth cerebral surface and a paucity of gyral and sulcal development, encompassing a spectrum of brain surface malformations ranging from complete agyria to subcortical band heterotopia (SBH). Classic lissencephaly is associated with an abnormally thick cortex, reduced or abnormal lamination, and diffuse neuronal heterotopia. SBH consists of circumferential bands of heterotopic neurons located just beneath the cortex and separated from it by a thin band of white matter. SBH represents the less severe end of the lissencephaly spectrum of malformations.

93. Loeys-Dietz syndrome; LDS

The Loeys-Dietz syndrome (LDS) is an autosomal dominant aortic aneurysm syndrome with widespread systemic involvement. The disorder is characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate. Some patients have craniofacial involvement consisting of cleft palate, craniosynostosis, or hypertelorism. Bifid uvula may also be present. The natural history is characterized by aggressive arterial aneurysms and a high rate of pregnancy-related complications.

93.1 Loeys-Dietz syndrome 1; LDS1 (OMIM 609192)

TGFBR1 gene (OMIM 190181) on chromosome 9q22; AD

A form of Loeys-Dietz syndrome.

93.2 Loeys-Dietz syndrome 2; LDS2 (OMIM 610168)

TGFBR2 gene (190182) on chromosome 3p24; AD

A form of Loeys-Dietz syndrome.

93.3 Loeys-Dietz syndrome 3; LDS3 (OMIM 613795)

SMAD3 gene (OMIM 603109) on chromosome 15q; AD

A form of Loeys-Dietz syndrome.

93.4 Loeys-Dietz syndrome 4; LDS4 (OMIM 614816)

TGFB2 gene (OMIM 190220) on chromosome 1q41; AD

A form of Loeys-Dietz syndrome.

94. Luscan-Lumish syndrome; LLS (OMIM 616831)

SETD2 gene (OMIM 612778) on chromosome 3p21; AD

Luscan-Lumish syndrome (LLS) is characterized by macrocephaly, intellectual disability, speech delay, low sociability, and behavioral problems. More variable features include postnatal overgrowth, obesity, advanced carpal ossification, developmental delay, and seizures.

95. Mandibulofacial dysostosis, Guion-Almeida type; MFDGA (OMIM 610536)

EFTUD2 gene (OMIM 603892) on chromosome 17q21; AD

Mandibulofacial dysostosis with microcephaly is a rare syndrome comprising progressive microcephaly, midface and malar hypoplasia, micrognathia, microtia, dysplastic ears, preauricular skin tags, significant

developmental delay, and speech delay. Many patients have major sequelae, including choanal atresia that results in respiratory difficulties, conductive hearing loss, and cleft palate.

96. Marfan syndrome; MFS (OMIM 154700)

FBN1 gene (OMIM 134797) on chromosome 15q21; AD

Marfan syndrome is a heritable disorder of fibrous connective tissue shows striking pleiotropism and clinical variability. The cardinal features occur in 3 systems: skeletal, ocular, and cardiovascular.

97. Marshall-Smith syndrome; MRSHSS (OMIM 602535)

NFIX gene (OMIM 164005) on chromosome 19p13; AD

The Marshall-Smith syndrome (MRSHSS) is a malformation syndrome characterized by accelerated skeletal maturation, relative failure to thrive, respiratory difficulties, mental retardation, and unusual facies, including prominent forehead, shallow orbits, blue sclerae, depressed nasal bridge, and micrognathia.

98. Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; MPPH

This disorder comprises megalencephaly, hydrocephalus, and polymicrogyria; polydactyly may also be seen. There is considerable phenotypic similarity between this disorder and the megalencephaly-capillary malformation syndrome (MCAP).

98.1 Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 1; MPPH1 (OMIM 603387)

PIK3R2 gene (OMIM 603157) on chromosome 19p13; AD

A form of Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome.

98.2 Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2; MPPH2 (OMIM 615937)

AKT3 gene (OMIM 611223) on chromosome 1q43-q44; AD

A form of Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome.

99. Menke-Hennekam syndrome; MKHK

Menke-Hennekam syndrome-1 (MKHK1) is a congenital disorder characterized by variable impairment of intellectual development and facial dysmorphisms. Feeding difficulties, autistic behavior, recurrent upper airway infections, hearing impairment, short stature, and microcephaly are also frequently seen.

99.1 Menke-Hennekam syndrome 1; MKHK1 (OMIM 618332)

CREBBP gene (OMIM 600140) on chromosome 16p13; AD

A form of Menke-Hennekam syndrome.

99.2 Menke-Hennekam syndrome 2; MKHK2 (OMIM 618333)

EP300 gene (OMIM 602700) on chromosome 22q13; AD

A form of Menke-Hennekam syndrome.

100. Metaphyseal dysplasia with maxillary hypoplasia with or without brachydactyly; MDMHB (OMIM 156510)

RUNX2 gene (OMIM 600211) on chromosome 6p21; AD

Metaphyseal dysplasia and maxillary hypoplasia with or without brachydactyly (MDMHB) is an autosomal dominant bone dysplasia characterized by metaphyseal flaring of long bones, enlargement of the medial halves of the clavicles, maxillary hypoplasia, variable brachydactyly, and dystrophic teeth.

101. Mowat-Wilson syndrome; MOWS (OMIM 235730)

ZEB2 gene (OMIM 605802) on chromosome 2q22; AD

Mowat-Wilson syndrome (MOWS) is an autosomal dominant complex developmental disorder; individuals with functional null mutations present with impaired intellectual development, delayed motor development, epilepsy, and a wide spectrum of clinically heterogeneous features suggestive of neurocristopathies at the cephalic, cardiac, and vagal levels.

102. Muenke syndrome; MNKES (OMIM 602849)

FGFR3 gene (OMIM 134934) on chromosome 4p16; AD

Muenke syndrome is an autosomal dominant disorder characterized by uni- or bicoronal synostosis, macrocephaly, midfacial hypoplasia, and developmental delay. Other more variable features include thimble-shaped middle phalanges, brachydactyly, carpal/tarsal fusion, and deafness. The phenotype is variable and can range from no detectable clinical manifestations to complex findings.

103. Muscular dystrophy, congenital (OMIM 613205)

LMNA (OMIM 150330) on chromosome 1q22; AD

Muscular dystrophy, congenital is a form of congenital muscular dystrophy. Patients present at birth, or within the first few months of life, with hypotonia, muscle weakness and often with joint contractures.

104. Myhre syndrome; MYHRS (OMIM 139210)

SMAD4 gene (OMIM 600993) on chromosome 18q21; AD

Myhre syndrome (MYHRS) is a rare disorder characterized by imparied intellectual development, dysmorphic facial features, including microcephaly, midface hypoplasia, prognathism, and blepharophimosis, typical skeletal anomalies, including short stature, square body shape, broad ribs, iliac hypoplasia, brachydactyly, flattened vertebrae, and thickened calvaria, and cardiovascular defects with a striking fibroproliferative response to surgical intervention.

105. NESCAV syndrome; NESCAVS (OMIM 614255)

KIF1A gene (OMIM 601255) on chromosome 2q37; AD

NESCAV syndrome (NESCAVS) is a neurodegenerative disorder characterized by onset of features in infancy or early childhood. Affected individuals show global developmental delay with delayed walking or difficulty walking due to progressive spasticity mainly affecting the lower limbs and often leading to loss of independent ambulation. There is variably impaired intellectual development, speech delay, and learning disabilities and/or behavioral abnormalities. Additional features may include cortical visual impairment, often associated with optic atrophy, axonal peripheral neuropathy, seizures, dysautonomia, ataxia, and dystonia. Brain imaging often shows progressive cerebellar atrophy and thin corpus callosum. Some patients may show developmental regression, particularly of motor skills.

106. Neurodegeneration with brain iron accumulation 5; NBIA5 (OMIM 300894)

WDR45 (OMIM 300526) gene on chromosome Xp11; XLD

Neurodegeneration with brain iron accumulation 5 (NBIA5), sometimes referred to as 'static encephalopathy of childhood with neurodegeneration in adulthood (SENDA),' is an X-linked neurodegenerative disorder characterized by global developmental delay in early childhood that is essentially static, with slow motor and cognitive gains until adolescence or early adulthood. In young adulthood, affected individuals develop progressive dystonia, parkinsonism, extrapyramidal signs, and dementia resulting in severe disability. Brain MRI shows iron accumulation in the globus pallidus and substantia nigra. A characteristic finding is T1-weighted hyperintensity surrounding a central band of hypointensity in the substantia nigra. Cerebral and cerebellar atrophy are also observed.

107. Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language; NEDHSIL (OMIM 613443)

MEF2C gene (OMIM 600662) on chromosome 5q14.3; AD

Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language (NEDHSIL) is characterized by global developmental delay with hypotonia, poor motor development with limited walking, impaired intellectual development with poor or absent speech, and behavioral abnormalities. Almost all affected individuals demonstrate repetitive stereotypic hand movements that can be categorized as hyperkinetic and resembling those of Rett syndrome. About 80% of patients develop various types of seizures that may be refractory to treatment. Additional features may include dysmorphic facial features, particularly dysplastic ears, poor eye contact episodic hyperventilation, tendency to infection, and abnormalities on brain imaging, such as enlarged ventricles, thin corpus callosum, and delayed myelination.

108. Neurodevelopmental disorder with involuntary movements; NEDIM (OMIM 617493)

GNAO1 gene (OMIM 139311) on chromosome 16q13; AD

NEDIM is a neurodevelopmental and neurodegenerative disorder characterized by delayed psychomotor development and infantile or childhood onset of hyperkinetic involuntary movements, including chorea and athetosis. The abnormal movements can be severe, sometimes resulting in inability to sit, walk, speak, or eat. Hyperkinetic movements can be exacerbated by specific triggers, such as stress, illness, or high temperature. Some patients have brain abnormalities, such as cerebral atrophy or thin corpus callosum, and some patients may develop seizures.

109. Neurodevelopmental disorder with neonatal respiratory insufficiency, hypotonia, and feeding difficulties; NEDRIHF (OMIM 616158)

PURA gene (OMIM 600473) on chromosome 5q31; AD

Neurodevelopmental disorder with neonatal respiratory insufficiency, hypotonia, and feeding difficulties (NEDRIHF) is characterized by severe hypotonia at birth associated with respiratory difficulties, including apnea and hypoventilation, and feeding difficulties. Many infants require ventilatory support or feeding tubes. Affected patients have global developmental delay, often never achieving walking or speech, although the severity can be variable. Additional common features may include seizures, exaggerated startle reflex, abnormal movements, and dysmorphic facial features. Brain imaging often shows hypomyelination and parenchymal atrophy. A subset of patients may have systemic features, such as cardiac defects, scoliosis, endocrine anomalies, constipation, or cryptorchidism.

110. Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart; NEDBEH (OMIM 616975)

RERE gene (OMIM 605226) on chromosome 1p36; AD

Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart is an autosomal dominant syndrome characterized by onset in infancy of developmental delay, intellectual disability, and behavioral disorders, such as autism spectrum disorders. About half of patients have additional abnormalities, most commonly involving the eye, heart, and genitourinary system.

111. Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant; NDHMSD (OMIM 614254)

GRIN1 gene (OMIM 138249) on chromosome 9q34; AD

NDHMSD is a severe neurodevelopmental disorder characterized by profound developmental delay, severe intellectual disability with absent speech, muscular hypotonia, and a hyperkinetic movement disorder. Additional features may include cortical blindness, generalized cerebral atrophy, and seizures.

112. Neurodevelopmental disorder with spastic diplegia and visual defects; NEDSDV (OMIM 615075)

CTNNB1 gene (OMIM 116806) on chromosome 3p22; AD

Neurodevelopmental disorder with spastic diplegia and visual defects (NEDSDV) is characterized by global developmental delay, impaired intellectual development, axial hypotonia, and dysmorphic craniofacial features with microcephaly. Many patients have visual abnormalities, ranging from strabismus

to optic nerve atrophy and retinal abnormalities. Affected individuals also develop spasticity, particularly of the lower limbs, and may have behavioral abnormalities.

113. Neurofibromatosis, type 1; NF1 (OMIM 162200)

NF1 (OMIM 613113) on chromosome 17q11; AD

Neurofibromatosis type I (NF1) is an autosomal dominant disorder characterized by cafe-au-lait spots, Lisch nodules, and fibromatous tumors of the skin. Individuals with the disorder have increased susceptibility to the development of benign and malignant tumors. NF1 is sometimes referred to as 'peripheral neurofibromatosis.'

114. Neurofibromatosis, type 2 / Schwannomatosis, vestibular; NF2/ SWNV (OMIM 101000)

NF2 gene (OMIM 607379) on chromosome 22q12; AD

Vestibular schwannomatosis (SWNV), also known as neurofibromatosis type II (NF2), is an autosomal dominant multiple neoplasia syndrome characterized by the development of multiple benign nerve sheath tumors, called schwannomas, particularly affecting the vestibular nerve (usually bilaterally), but also involving cranial, spinal, and peripheral/cutaneous nerves. Meningiomas are common, affecting up to 80% of affected individuals. Ependymomas are seen in 20 to 35% of affected individuals. Ocular manifestations, including cataracts, retinal hamartomas, and epiretinal membranes, are also seen.

115. Nicolaides-Baraitser syndrome; NCBRS (OMIM 601358)

SMARCA2 gene (OMIM 600014) on chromosome 9p24; AD

Nicolaides-Baraitser syndrome (NCBRS) is characterized by severely impaired intellectual development, early-onset seizures, short stature, dysmorphic facial features, and sparse hair.

116. Noonan syndrome; NS

Noonan syndrome (NS) is an autosomal dominant disorder characterized by short stature, facial dysmorphism, and a wide spectrum of congenital heart defects. The distinctive facial features consist of a broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears. Cardiac involvement is present in up to 90% of patients. Pulmonic stenosis and hypertrophic cardiomyopathy are the most common forms of cardiac disease, but a variety of other lesions are also observed. Additional relatively frequent features include multiple skeletal defects (chest and spine deformities), webbed neck, mental retardation, cryptorchidism, and bleeding diathesis.

116.1 Noonan syndrome 1; NS1 (OMIM 163950)

PTPN11 gene (OMIM 176876) on chromosome 12q24; AD

A form of Noonan syndrome.

116.2 Noonan syndrome 3; NS3 (OMIM 609942)

KRAS gene (OMIM 190070) on chromosome 12p12; AD

A form of Noonan syndrome.

116.3 Noonan syndrome 4; NS4 (OMIM 610733)

SOS1 gene (OMIM 182530) on chromosome 2p22; AD

A form of Noonan syndrome.

116.4 Noonan syndrome 5; NS5 (OMIM 611553)

RAF1 gene (OMIM 164760) on chromosome 3p25; AD

A form of Noonan syndrome.

116.5 Noonan syndrome 6; NS6 (OMIM 613224)

NRAS gene (OMIM 164790) on chromosome 1p13; AD

A form of Noonan syndrome.

116.6 Noonan syndrome 7; NS7 (OMIM 613706)

BRAF gene (OMIM 164757) on chromosome 7q34; AD

A form of Noonan syndrome.

116.7 Noonan syndrome 8; NS8 (OMIM 615355)

RIT1 gene (OMIM 609591) on chromosome 1q22; AD

A form of Noonan syndrome.

116.8 Noonan syndrome 9; NS9 (OMIM 616559)

SOS2 gene (OMIM 601247) on chromosome 14q21; AD

A form of Noonan syndrome.

116.9 Noonan syndrome 10; NS10 (OMIM 616564)

LZTR1 gene (OMIM 600574) on chromosome 22q11; AD

A form of Noonan syndrome.

117. Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia; NSLL (OMIM 613563)

CBL gene (OMIM 165360) on chromosome 11q23; AD

Noonan syndrome-like disorder is a developmental disorder resembling Noonan syndrome and characterized by facial dysmorphism, a wide spectrum of cardiac disease, reduced growth, variable cognitive deficits, and ectodermal and musculoskeletal anomalies. There is extensive phenotypic heterogeneity and variable expressivity. Patients with heterozygous germline CBL mutations have an increased risk for certain malignancies, particularly juvenile myelomonocytic leukemia.

118. Noonan syndrome-like with loose anagen hair 1; NSLH1 (OMIM 607721)

SHOC2 gene (OMIM 602775) on chromosome 10q25; AD

Noonan syndrome-like disorder with loose anagen hair is characterized by facial features similar to those observed in Noonan syndrome, including hypertelorism, ptosis, downslanting palpebral fissures, low-set posteriorly angulated ears, and overfolded pinnae. In addition, patients display short stature, frequently with growth hormone deficiency; cognitive deficits; relative macrocephaly; small posterior fossa resulting in Chiari I malformation; hypernasal voice; cardiac defects, especially dysplasia of the mitral valve and septal defects; and ectodermal abnormalities, in which the most characteristic feature is the hair anomaly, including easily pluckable, sparse, thin, slow-growing hair.

119. Opitz GBBB Syndrome, Type II / Teebi hypertelorism syndrome 1; TBHS1 (OMIM 145420)

SPECC1L gene (OMIM 614140) on chromosome 22q11; AD

Teebi hypertelorism syndrome-1 (TBHS1) is an autosomal dominant disorder characterized by hypertelorism with upslanting palpebral fissures, prominent forehead, broad and depressed nasal bridge with short nose, thick eyebrows, and widow's peak. Additional features include small broad hands with mild interdigital webbing and shawl scrotum. Umbilical malformations, cardiac defects, natal teeth, cleft lip/palate, congenital diaphragmatic hernia, and malformations of the central nervous system (ventriculomegaly, abnormal corpus callosum) have also been reported. Development is typically normal, although some patients with developmental delays have been reported.

120. Osteogenesis imperfecta; OI

Osteogenesis imperfecta (OI) is a connective tissue disorder characterized by bone fragility and low bone mass. Due to considerable phenotypic variability, Sillence et al. (1979)developed a classification of OI subtypes based on clinical features and disease severity: OI type I, with blue sclerae; perinatal lethal OI type II, also known as congenital OI; OI type III, a progressively deforming form with normal sclerae; and OI type IV, with normal sclerae.

120.1 Osteogenesis imperfecta, type I; OI1 (OMIM 166200)

COL1A1 gene (OMIM 120150) on chromosome 17q21; AD

A form of Osteogenesis imperfecta.

120.2 Osteogenesis imperfecta, type II; OI2 (OMIM 166210)

COL1A1 gene (OMIM 120150) on chromosome 17q21 or the COL1A2 gene (120160) on chromosome 17q21; AD

A form of Osteogenesis imperfecta.

120.3 Osteogenesis imperfecta, type III; OI3 (OMIM 259420)

COL1A1 gene (OMIM 120150) on chromosome 17q21 or the COL1A2 gene (120160) on chromosome 17q21; AD

A form of Osteogenesis imperfecta.

120.4 Osteogenesis imperfecta, type IV; OI4 (OMIM 166220)

COL1A1 gene (OMIM 120150) on chromosome 17q21 or the COL1A2 gene (120160) on chromosome 17q21; AD

A form of Osteogenesis imperfecta.

120.5 Osteogenesis imperfecta, type V; O5 (OMIM 610967)

IFITM5 gene (OMIM 614757) on chromosome 11p15; AD

A form of Osteogenesis imperfecta.

121. Otopalatodigital syndrome, type II; OPD2 (OMIM 304120)

FLNA gene (OMIM 300017) on chromosome Xq28; XLD

Otopalatodigital syndrome-2 is 1 of 4 otopalatodigital syndromes caused by mutations in the FLNA gene. The disorders, which include frontometaphyseal dysplasia (FMD1), otopalatodigital syndrome-1 (OPD1), and Melnick-Needles syndrome (MNS), constitute a phenotypic spectrum. At the mild end of the spectrum, males with OPD1 have cleft palate and mild skeletal anomalies with conductive deafness caused by ossicular anomalies. FMD is characterized by a generalized skeletal dysplasia, deafness and urogenital defects. Males with OPD2 have disabling skeletal anomalies in addition to variable malformations in the hindbrain, heart, intestines, and kidneys that frequently lead to perinatal death. The most severe phenotype, MNS, is characterized by a skeletal dysplasia in the heterozygote. Affected males exhibit severe malformations similar to those observed in individuals with OPD2, resulting in prenatal lethality or death in the first few months of life.

122. Overgrowth syndrome and/or cerebral malformations

PIK3CA gene (OMIM 171834) on chromosome 3q26; AD

Overgrowth syndrome and/or cerebral malformations is a PIK3CA-related disorders with a range of clinical findings in which the core features are congenital or early-childhood onset of segmental/focal overgrowth with or without cellular dysplasia. The predominant areas of overgrowth include the brain, limbs, trunk, and face, all usually in an asymmetric distribution. Generalized brain overgrowth may be accompanied by secondary overgrowth of specific brain structures resulting in ventriculomegaly, a markedly thick corpus callosum, and cerebellar tonsillar ectopia with crowding of the posterior fossa. Vascular malformations may include capillary, venous, and less frequently, arterial or mixed malformations. Lymphatic malformations may be in various locations and can cause various clinical issues, including swelling, pain, and occasionally localized bleeding secondary to trauma. Lipomatous overgrowth may occur ipsilateral or contralateral to a vascular malformation, if present. The degree of intellectual disability appears to be mostly related to the presence and severity of seizures, cortical dysplasia, and hydrocephalus.

123. Parietal foramina with cleidocranial dysplasia; PFMCCD (OMIM 168550)

MSX2 gene (123101) on chromosome 5q35; AD

Parietal foramina are symmetric, oval defects in the parietal bone situated on each side of the sagittal suture and separated from each other by a narrow bridge of bone. The size of the openings decrease with age and considerable intrafamilial variability is observed. The main clinical features of cleidocranial dysplasia include persistently open skull sutures with bulging calvaria, hypoplasia or aplasia of the clavicles permitting abnormal facility in apposing the shoulders, wide pubic symphysis, short middle phalanx of the fifth fingers, dental anomalies, and often vertebral malformation.

124. Pfeiffer syndrome (OMIM 101600)

FGFR1 gene (OMIM 136350) on chromosome 8q11 or in the FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

Pfeiffer syndrome is an autosomal dominant craniosynostosis syndrome with characteristic anomalies of the hands and feet. Three clinical subtypes, which have important diagnostic and prognostic implications, have been identified. Type 1, the classic syndrome, is compatible with life and consists of craniosynostosis, midface deficiency, broad thumbs, broad great toes, brachydactyly, and variable syndactyly. Type 2 consists of cloverleaf skull with Pfeiffer hands and feet, together with ankylosis of the elbows. Type 3 is similar to type 2 but without cloverleaf skull. Ocular proptosis is severe, and the anterior cranial base is markedly short. Various visceral malformations have been found in association with type 3. Early demise is characteristic of types 2 and 3.

125. Phelan-McDermid syndrome; PHMDS (OMIM 606232)

SHANK3 gene (OMIM 606230) on chromosome 22q13; AD

Phelan-McDermid syndrome (PHMDS) is a developmental disorder with variable features. Common features include neonatal hypotonia, global developmental delay, normal to accelerated growth, absent to severely delayed speech, autistic behavior, and minor dysmorphic features.

126. Pierpont syndrome; PRPTS (OMIM 602342)

TBL1XR1 gene (OMIM 608628) on chromosome 3q26; AD

Pierpont syndrome (PRPTS) is a multiple congenital anomaly syndrome associated with learning disability. Key features include distinctive facial characteristics, especially when smiling, plantar fat pads, and other limb anomalies.

127. Pitt-Hopkins syndrome; PTHS (OMIM 610954)

TCF4 gene (OMIM 602272) on chromosome 18q21; AD

The Pitt-Hopkins syndrome is characterized by mental retardation, wide mouth and distinctive facial features, and intermittent hyperventilation followed by apnea.

128. Platyspondylic skeletal dysplasia, Torrance type; PLSDT (OMIM 151210)

COL2A1 gene (OMIM 120140) on chromosome 12q13; AD

The Torrance type of platyspondylic lethal skeletal dysplasia (PLSDT) is an autosomal dominant disorder characterized by varying platyspondyly, short ribs with anterior cupping, hypoplasia of the lower ilia with broad ischial and pubic bones, and shortening of the tubular bones with splayed and cupped metaphyses. Histology of the growth plate typically shows focal hypercellularity with slightly enlarged chondrocytes in the resting cartilage and relatively well-preserved columnar formation and ossification at the chondroosseous junction. Though generally lethal in the perinatal period, longer survival has been reported.

129. Porencephaly 1 / Brain small vessel disease with or without ocular anomalies; BSVD1 (OMIM 175780)

COL4A1 gene (OMIM 120130) on chromosome 13q34; AD

Brain small vessel disease-1 (Porencephaly 1) is an autosomal dominant disorder with variable manifestations resulting from disruption of vascular basement membranes, particularly in the cerebral vasculature. The increased fragility of these vessels render them susceptible to hemorrhage, as early as in utero or by birth trauma, although the risk remains throughout life and some patients may present in

adulthood. This genetic predisposition may extend beyond hemorrhagic stroke to include retinal and renal vascular defects. Clinical features thus reflect the location and severity of the vascular defect, including impaired neurologic development or function, hemiplegia, seizures, and variable ocular anomalies. The disturbed vasculature leads to cerebral degeneration, and brain imaging typically shows 'porencephaly,' hemosiderin deposition, calcifications, lacunar infarcts, enlarged ventricles, and leukoencephalopathy. Some patients may show 'schizencephaly' on brain imaging, which is also attributed to encephaloclastic processes, such as vascular injury.

130.Primrose syndrome; PRIMS (OMIM 259050)

ZBTB20 gene (OMIM 606025) on chromosome 3q13; AD

Primrose syndrome (PRIMS) consists of recognizable facial features, macrocephaly, mental retardation, enlarged and calcified external ears, sparse body hair, and distal muscle wasting.

131.Pseudoachondroplasia; PSACH (OMIM 177170)

COMP gene (OMIM 600310) on chromosome 19p13; AD

Pseudoachondroplasia (PSACH) is an autosomal dominant osteochondrodysplasia characterized by disproportionate short stature, deformity of the lower limbs, brachydactyly, loose joints, and ligamentous laxity. Vertebral anomalies, present in childhood, usually resolve with age, but osteoarthritis is progressive and severe.

132.Rett syndrome; RTT (OMIM 312750)

MECP2 (OMIM 300005) on chromosome Xq28; AD

Rett syndrome is a neurodevelopmental disorder that occurs almost exclusively in females. It is characterized by arrested development between 6 and 18 months of age, regression of acquired skills, loss of speech, stereotypic movements (classically of the hands), microcephaly, seizures, and mental retardation. Rarely, classically affected males with somatic mosaicism or an extra X chromosome have been described.

133.Rett syndrome, congenital variant (OMIM 613454)

FOXG1 gene (OMIM 164874) on chromosome 14q13; AD

The congenital variant of Rett syndrome is a severe neurodevelopmental disorder with features of classic Rett syndrome, but earlier onset in the first months of life.

134.Robinow-Sorauf syndrome (OMIM 180750)

TWIST gene (TWIST1; 601622) on chromosome 7p21; AD

Robinow-Sorauf syndrome is an autosomal dominant syndrome characterized by craniosynostosis, asymmetry of orbits, flat face, hypertelorism, a thin, long, and pointed nose, shallow orbits, strabismus, and broad great toes with a duplication of the distal phalanx. RSS is clinically similar to Saethre-Chotzen syndrome, with the most characteristic additional feature in Robinow-Sorauf syndrome being a bifid or partially duplicated hallux.

135.Rubinstein-Taybi syndrome; RSTS

Rubinstein-Taybi syndrome is a multiple congenital anomaly syndrome characterized by mental retardation, postnatal growth deficiency, microcephaly, broad thumbs and halluces, and dysmorphic facial features. The facial appearance is striking, with highly arched eyebrows, long eyelashes, downslanting palpebral fissures, broad nasal bridge, beaked nose with the nasal septum, highly arched palate, mild micrognathia, and characteristic grimacing or abnormal smile. Affected individuals also have an increased risk of tumor formation.

135.1 Rubinstein-Taybi syndrome 1; RSTS1 (OMIM 180849)

CREBBP gene (OMIM 600140) on chromosome 16p13; AD

A form of Rubinstein-Taybi syndrome.

135.2 Rubinstein-Taybi syndrome 2; RSTS2 (OMIM 613684)

EP300 gene (OMIM 602700) on chromosome 22q13; AD

A form of Rubinstein-Taybi syndrome.

136. SADDAN dysplasia; SADDAN (OMIM 616482)

FGFR3 gene (OMIM 134934) on chromosome 4p16; AD

Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is a very rare skeletal dysplasia characterized by the constellation of these features. Radiology reveals 'ram's horn' shaped clavicles and reverse bowing of lower limbs. Approximately half of patients die before the fourth week of life secondary to respiratory failure.

137. Saethre-Chotzen syndrome; SCS (OMIM 101400)

FGFR2 gene (OMIM 176943) on chromosome 10q26; AD

Saethre-Chotzen syndrome (SCS) is characterized by craniosynostosis, facial dysmorphism, and hand and foot abnormalities. Coronal synostosis resulting in brachycephaly is the most frequent cranial abnormality observed, and the most common facial features are asymmetry, hypertelorism, and maxillary hypoplasia. Other features include high forehead, low frontal hairline, late-closing fontanel, strabismus, ptosis, lacrimal duct stenosis, deviated nasal septum, small low-set posteriorly rotated ears with prominent crus, and hearing loss. The limb anomalies consist of radioulnar synostosis, brachydactyly, cutaneous syndactyly, and hallux valgus. Patients also exhibit short stature and vertebral fusion, and mild to moderate mental retardation has been noted in some cases. Inter- and intrafamilial variability is significant, with some patients having fusion of other sutures, or no apparent craniosynostosis but abnormal skull morphology. The degree of syndactyly is also variable, and digital abnormalities can be absent.

138. Saethre-Chotzen syndrome with or without eyelid anomalies; SCS (OMIM 101400)

TWIST1 gene (OMIM 601622) on chromosome 7p21; AD

Saethre-Chotzen syndrome is characterized by craniosynostosis, facial dysmorphism, and hand and foot abnormalities. Coronal synostosis resulting in brachycephaly is the most frequent cranial abnormality observed, and the most common facial features are asymmetry, hypertelorism, and maxillary hypoplasia. Other features include high forehead, low frontal hairline, late-closing fontanel, strabismus, ptosis, lacrimal duct stenosis, deviated nasal septum, small low-set posteriorly rotated ears with prominent crus, and hearing loss. The limb anomalies consist of radioulnar synostosis, brachydactyly, cutaneous syndactyly, and hallux valgus. Patients also exhibit short stature and vertebral fusion, and mild to moderate mental retardation has been noted in some cases. Inter- and intrafamilial variability is significant, with some patients having fusion of other sutures, or no apparent craniosynostosis but abnormal skull morphology. The degree of syndactyly is also variable, and digital abnormalities can be absent.

139. SBBYSS syndrome; SBBYSS (OMIM 603736)

KAT6B gene (OMIM 605880) on chromosome 10q22; AD

Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS), a variant of Ohdo syndrome (249620), is characterized by distinctive facial appearance with severe blepharophimosis, an immobile mask-like face, a bulbous nasal tip, and a small mouth with a thin upper lip. The condition presents in infancy with severe hypotonia and feeding problems. Associated skeletal problems include joint laxity, abnormally long thumbs and great toes, and dislocated or hypoplastic patellae. Structural cardiac defects are present in around 50% of cases, and dental anomalies, including small and pointed teeth, are common. Many affected individuals have abnormalities of thyroid structure or function. YSS is usually associated with severe mental retardation, delayed motor milestones, and significantly impaired speech.

140. Schinzel-Giedion syndrome / Schinzel-Giedion midface retraction syndrome; SGS (OMIM 269150)

SETBP1 gene (OMIM 611060) on chromosome 18q12; AD

Schinzel-Giedion syndrome is a highly recognizable syndrome characterized by severe mental retardation, distinctive facial features, and multiple congenital malformations including skeletal abnormalities, genitourinary and renal malformations, and cardiac defects, as well as a higher-than-normal prevalence of tumors, notably neuroepithelial neoplasia.

141. Schuurs-Hoeijmakers syndrome; SHMS (OMIM 615009)

PACS1 gene (OMIM 607492) on chromosome 11q13; AD

Schuurs-Hoeijmakers syndrome (SHMS) is characterized by impaired intellectual development, distinct craniofacial features, and variable additional congenital abnormalities.

142. SED congenita; SEDC (OMIM 183900)

COL2A1 gene (OMIM 120140) on chromosome 12q13; AD

Spondyloepiphyseal dysplasia congenita (SEDC) is an autosomal dominant chondrodysplasia characterized by disproportionate short stature (short trunk), abnormal epiphyses, and flattened vertebral bodies. Skeletal features are manifested at birth and evolve with time. Other features include myopia and/or retinal degeneration with retinal detachment and cleft palate.

143. Shprintzen-Goldberg syndrome; SGS (OMIM 182212)

SKI gene (OMIM 164780) on chromosome 1p36; AD

Shprintzen-Goldberg syndrome (SGS) is a disorder comprising craniosynostosis, a marfanoid habitus, and skeletal, neurologic, cardiovascular, and connective tissue anomalies. There appears to be a characteristic facies involving hypertelorism, downslanting palpebral fissures, high-arched palate, micrognathia, and low-set posteriorly rotated ears. Other commonly reported manifestations include hypotonia, developmental delay, and inguinal or umbilical hernia; the most common skeletal manifestations are arachnodactyly, pectus deformity, camptodactyly, scoliosis, and joint hypermobility.

144. Sotos syndrome; SOTOS (OMIM 117550)

NSD1 gene (OMIM 606681) on chromosome 5q35; AD

Sotos syndrome (SOTOS) is a neurologic disorder characterized by overgrowth from the prenatal stage through childhood, with advanced bone age, an unusual face with large skull, acromegalic features and pointed chin, occasional brain anomalies and seizures, and impaired intellectual development.

145. Spinal muscular atrophy, lower extremity-predominant, 2B, autosomal dominant; SMALED2B (OMIM 618291)

BICD2 gene (OMIM 609797) on chromosome 9q22; AD

SMALED2B is a severe neuromuscular disorder with onset in utero. Affected individuals show decreased fetal movements and are usually born with congenital contractures consistent with arthrogryposis multiplex congenita (AMC). After birth, they have severe hypotonia and muscle atrophy as well as respiratory insufficiency due to muscle weakness. Some patients may have dysmorphic facial features and/or abnormalities on brain imaging. Many patients die in early childhood.

146. Stickler syndrome; STL

Stickler syndrome (STL) is a clinically variable and genetically heterogeneous disorder characterized by ocular, auditory, skeletal, and orofacial abnormalities. Most forms of Stickler syndrome are characterized by the eye findings of high myopia, vitreoretinal degeneration, retinal detachment, and cataracts. Additional findings may include midline clefting (cleft palate or bifid uvula), Pierre Robin sequence, flat midface, sensorineural or conductive hearing loss, mild spondyloepiphyseal dysplasia, and early-onset osteoarthritis.

146.1 Stickler syndrome, type I; STL1 (OMIM 108300)

COL2A1 gene (OMIM 120140) on chromosome 12q13; AD

A form of Stickler syndrome.

146.2 Stickler syndrome, type II (OMIM 604841)

COL11A1 gene (OMIM 120280) on chromosome 1p21; AD

A form of Stickler syndrome.

147. Sweeney-Cox syndrome; SWCOS (OMIM 617746)

TWIST1 gene (OMIM 601622) on chromosome 7p21; AD

Sweeney-Cox syndrome (SWCOS) is characterized by striking facial dysostosis, including hypertelorism, deficiencies of the eyelids and facial bones, cleft palate/velopharyngeal insufficiency, and low-set cupped ears.

148. Symmetric circumferential skin creases, congenital, 1; CSCSC1 (OMIM 156610)

TUBB gene (OMIM 191130) on chromosome 6p21; AD

Congenital symmetric circumferential skin creases (CSCSC) is characterized by the folding of excess skin, which leads to ringed creases, primarily of the limbs. Affected individuals also exhibit intellectual disability, cleft palate, and dysmorphic features.

149. Thanatophoric dysplasia; TD

Thanatophoric dysplasia (TD) is a severe short-limb dwarfism syndrome that is usually lethal in the perinatal period. Norman et al. (1992) classified cases of TD into subtypes based on the presence of curved as opposed to straight femurs; patients with straight, relatively long femurs always had associated severe cloverleaf skull and were designated TD type II (TD2), while TD cases with curved, short femurs with or without cloverleaf skull were designated TD type I (TD1).

149.1 Thanatophoric dysplasia, type I; TD1 (OMIM 187600)

FGFR3 gene (OMIM 134934) on chromosome 4p16; AD

A form of Thanatophoric dysplasia.

149.2 Thanatophoric dysplasia, type II; TD2 (OMIM 187601)

FGFR3 gene (OMIM 134934) on chromosome 4p16; AD

A form of Thanatophoric dysplasia.

150. Trichorhinophalangeal syndrome, type I; TRPS1 (OMIM 190350)

TRPS1 gene (OMIM 604386) on chromosome 8q23; AD

Trichorhinophalangeal syndrome type I (TRPS1) is an autosomal dominant malformation syndrome characterized by distinctive craniofacial and skeletal abnormalities. TRPS I patients have sparse scalp hair, bulbous tip of the nose, long flat philtrum, thin upper vermilion border, and protruding ears. Skeletal abnormalities include cone-shaped epiphyses at the phalanges, hip malformations, and short stature.

151. Trigonocephaly; TRIGNO

Individuals with trigonocephaly have a keel-shaped forehead with wide biparietal diameter, resulting in a triangular shape of the head. Trigonocephaly results from premature closure of the metopic sutures and usually occurs sporadically.

151.1 Trigonocephaly 1; TRIGNO1 (OMIM 190440)

FGFR1 gene (OMIM 136350) on chromosome 8p11; AD

A form of Trigonocephaly.

151.2 Trigonocephaly 2; TRIGNO2 (OMIM 614485)

FREM1 gene (OMIM 608944) on chromosome 9p22; AD

A form of Trigonocephaly.

152. Tuberous sclerosis; TSC

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder characterized by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, and lung. Central nervous system manifestations include epilepsy, learning difficulties, behavioral problems, and autism. Renal lesions, usually angiomyolipomas, can cause clinical problems secondary to hemorrhage or by compression and replacement of healthy renal tissue, which can cause renal failure. Patients can also develop renal cysts and renal-cell carcinomas. Pulmonary lymphangioleiomyomatosis can develop in the lungs. Skin lesions include melanotic macules, facial angiofibromas, and patches of connective tissue nevi. There is a wide clinical spectrum, and some patients may have minimal symptoms with no neurologic disability.

152.1 Tuberous sclerosis-1; TSC1 (OMIM 191100)

TSC1 gene (OMIM 605284) on chromosome 9q34; AD

A form of Tuberous sclerosis.

152.2 Tuberous sclerosis-2; TSC2 (OMIM 613254)

TSC2 gene (OMIM 191092) on chromosome 16p13; AD

A form of Tuberous sclerosis.

153. Visceral myopathy 1; VSCM1 (OMIM 155310)

ACTG2 gene (OMIM 102545) on chromosome 2p13; AD

Familial visceral myopathy (VSCM) is a rare inherited form of myopathic pseudoobstruction, characterized by impaired function of enteric smooth muscle cells resulting in abnormal intestinal mobility, severe abdominal pain, malnutrition, and even death (Lehtonen et al., 2012). Visceral myopathy represents a phenotypic spectrum of disease characterized by inter- and intrafamilial variability, in which the most severely affected patients exhibit prenatal bladder enlargement, intestinal malrotation, neonatal functional gastrointestinal obstruction, and chronic dependence on total parenteral nutrition (TPN) and urinary catheterization.

154. Wieacker-Wolff syndrome, female-restricted; WRWFFR (OMIM 301041)

ZC4H2 gene (OMIM 300897) on chromosome Xq11; XLD

Female-restricted Wieacker-Wolff syndrome (WRWFFR) is an X-linked dominant syndromic form of neurogenic arthrogryposis multiplex congenita (AMC) with central and peripheral nervous system involvement. Affected individuals have decreased fetal movements causing the development of contractures in utero and resulting in AMC and diffuse contractures involving the large and small joints apparent at birth. There is global developmental delay with difficulty walking or inability to walk, hypotonia that often evolves to spasticity, and variably impaired intellectual development with poor or absent speech and language. Dysmorphic facial features, including hypotonic facies, ptosis, microretrognathia, and small mouth, are seen in most patients. Seizures are uncommon; some patients have evidence of a peripheral motor neuropathy with distal muscle weakness. The level of X inactivation in lymphocytes and fibroblasts is often skewed, but may not predict the severity of the phenotype.

155. Wiedemann-Steiner syndrome; WDSTS (OMIM 605130)

KMT2A gene (OMIM 159555) on chromosome 11q23; AD

Wiedemann-Steiner syndrome (WDSTS) is a congenital malformation syndrome characterized by hypertrichosis cubiti associated with short stature; consistent facial features, including long eyelashes, thick or arched eyebrows with a lateral flare, broad nasal bridge, and downslanting and vertically narrow palpebral fissures; mild to moderate intellectual disability; behavioral difficulties; and hypertrichosis on the back.