

ACHONDROPLASIA; ACH / OMIM 2010

INHERITANCE:

Autosomal dominant

GROWTH :

Height

Short-limb dwarfism identifiable at birth

Mean male adult height, 131cm

Mean female height, 124 cm



HEAD AND NECK:

Head

Frontal bossing

Megalencephaly

Face

Midface hypoplasia

Ears

Recurrent otitis media in infancy and childhood

Conductive hearing loss

Nose

Low nasal bridge

RESPIRATORY:

Upper airway obstruction

SKELETAL:

Generalized joint laxity

Skull

Foramen magnum stenosis

Spine

Lumbar kyphosis in infancy

Exaggerated lumbar lordosis during childhood and adulthood

Congenital spinal stenosis due to short pedicles, especially lumbar

Progressive interpediculate narrowing in lumbar spine

Pelvis

Dysplastic ilium

Narrow sacroiliac groove

Flat rooted acetabulae

Limbs

Bowing of legs

Rhizomelic shortening

Short femoral neck



Metaphyseal flaring
Limited elbow and hip extension



Hands

Brachydactyly
Trident hand

NEUROLOGIC:

Hydrocephalus, occasional
Hypotonia in infancy and early childhood
Brain stem compression
Delayed motor development



MISCELLANEOUS:

Autosomal dominant with complete penetrance
80% cases new mutations
99+% of the mutations are FGFR3, G380R
([134934.0001](#))



Paternal age effect

MOLECULAR BASIS:

Caused by mutation in the fibroblast growth factor receptor-3 gene (FGFR3, [134934.0001](#))

MOSTAFA ELBABA

ALAGILLE SYNDROME; ALGS / OMIM 2010

INHERITANCE:

Autosomal dominant



GROWTH:

Failure to thrive

HEAD AND NECK:

Face

Broad forehead

Triangular face

Prominent zygomatic arch

Eyes



Deep-set eyes

Posterior embryotoxon

Anterior chamber anomalies

Eccentric or ectopic pupils

Chorioretinal atrophy



Retinal pigment clumping

Axenfeld anomaly

Choroidal folds

Strabismus

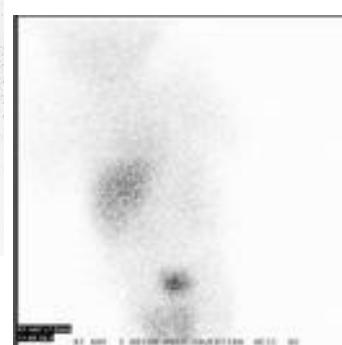
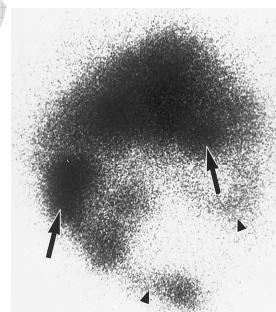
Myopia

Anomalous optic disc

Nose

Long nose with bulbous tip

CARDIOVASCULAR:



Peripheral pulmonary artery stenosis

Atrial septal defect

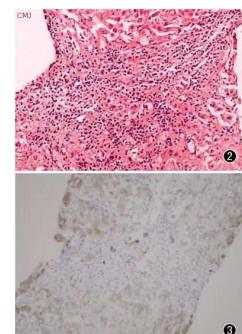
Ventricular septal defect

Coarctation of aorta

CHEST:

Ribs, sternum, clavicles, and scapulae

Rib anomalies



ABDOMEN:

Liver

Cholestasis

Intrahepatic duct deficiency

Biliary tract

Extrahepatic duct involvement

SKELETAL:

Spine

- Vertebral anomalies
- Butterfly vertebral arch
- Hemivertebrae

Limbs

- Short ulnae
- Hands
 - Short distal phalanges



NEUROLOGIC:

Central nervous system

- Mild mental retardation, occasional
- Learning disability

Peripheral nervous system

- Absent deep tendon reflexes



GENITOURINARY:

Kidneys

- Renal dysplasia
- Renal mesangiolipidosis
- Medullary cystic disease



NEOPLASIA:

- Hepatocellular carcinoma
- Papillary thyroid carcinoma

LABORATORY:

- Hypercholesterolemia
- Hypertriglyceridemia
- Elevated transaminases
- Abnormal liver function tests

A

B

C

D

MOLECULAR:

Caused by mutation in the jagged 1 gene (JAG1, [601920.0001](#))



MOSTAFA ELBABA

ANGELMAN SYNDROME; AS / OMIM 2010

INHERITANCE:

Isolated cases

GROWTH:

Obesity (older children)

HEAD AND NECK:

Head

Microcephaly, postnatal

Brachycephaly

Flat occiput

Occipital groove

Face

Prognathia

Eyes

Strabismus

Mouth

Protruding tongue

Macrostomia

Excessive drooling

Eyes

Decreased pigmentation of choroid and iris

Teeth

Widely spaced teeth

ABDOMEN:

Gastrointestinal

Feeding difficulties in neonatal period

Excessive chewing/mouthing behaviors

Abnormal food-related behaviors

Constipation

SKELETAL:

Scoliosis

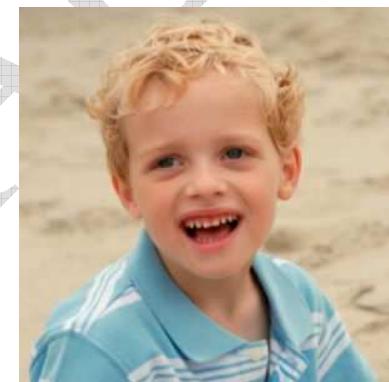
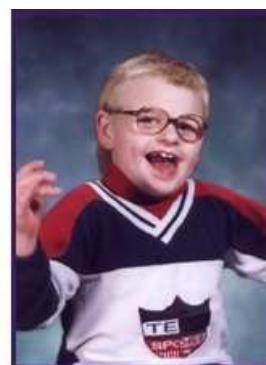
SKIN, NAILS, HAIR:

Hypopigmentation (seen only in deletion cases)

NEUROLOGIC:

Central nervous system

Developmental delay



Severe mental retardation
Absent speech
Ataxia with jerky arm movements
Wide-based gait
Clumsiness, unsteadiness
Tremor of limbs
Hypotonia
Seizures
Hyperreflexia



Characteristic arm position with wrist and elbow flexion

Abnormal sleep-wake cycles

Decreased need for sleep

Characteristic electroencephalogram (EEG) discharges

Mild cortical atrophy on CT or MRI

Behavioral/psychiatric manifestations

Paroxysmal laughter

Easily excitable

Attraction to/fascination with water, crinkly items (paper, plastic)



MISCELLANEOUS:

Onset between 6 and 12 months of age

Increased sensitivity to heat

70% due to de novo maternal deletion of 15q11.2-q13

2% due to paternal uniparental disomy of 15q11.2-q13

2-3% due to imprinting defects

25% due to mutations in UBE3A ([601623](#))



MOLECULAR:

Caused by mutation in the ubiquitin protein ligase E3A gene
(UBE3A, [601623.0001](#))



MOSTAFA ELBABA

BECKWITH-WIEDEMANN SYNDROME / BWS OMIM 2008

Clinical Synopsis

INHERITANCE :

Autosomal dominant

GROWTH :

Height

Average birth length, 52.6cm

Growth parallels curve at or above 95%

Weight

Average birth weight 4kg

Other

Generalized overgrowth

Hemihypertrophy

HEAD AND NECK :

Head

Metopic ridge

Large fontanelle

Prominent occiput



Beckwith-Wiedemann syndrome



Microcephaly



Macroglossia



Umbilical hernia

Face

Coarse facial features

Eyes

Prominent

Ears

Linear ear lobe creases

Posterior helical indentations



©ADAM

Mouth

Macroglossia



CARDIOVASCULAR :

Heart

Cardiomyopathy

Cardiomegaly

ABDOMEN :

External features

Omphalocele (exomphalos)

Diastasis recti

Liver

Hepatomegaly

Pancreas

Pancreatic hyperplasia

GENITOURINARY :

External genitalia, male

Overgrowth of external genitalia

External genitalia, female

Overgrowth of external genitalia

Internal genitalia, male

Cryptorchidism

Kidneys

Renal medullary dysplasia

Large kidneys



SKELETAL :

Advanced bone age, most pronounced during first 4 years

METABOLIC :

Neonatal hypoglycemia

ENDOCRINE FEATURES :

Adrenocortical cytomegaly

Pituitary amphophil hyperplasia

NEOPLASIA :

Wilms tumor

Hepatoblastoma

Adrenal carcinoma

Gonadoblastoma



LABORATORY ABNORMALITIES :

Caused by duplication or deletion at 11p15.5

MISCELLANEOUS :

Genetic heterogeneity

Most cases are isolated

Imprinting at 11p15.5

DIAGNOSIS

Diagnosis is based on clinical findings. A careful cytogenetic analysis of the 11p15 region is recommended. Prenatal diagnosis by ultrasonography is possible.

MOLECULAR GENETICS

1. Mutation in the cyclin-dependent kinase inhibitor 1C gene (CDKN1C, 600856.0001)
2. Mutation in the nuclear receptor binding SET domain protein 1 (NSD1, 606681.0011)
3. Mutation in the H19 gene (H19, 103280.0001)
4. Mutation in the KCNQ1-overlapping transcript 1 gene (KCNQ10T1, 604115.0001)

BLOOM SYNDROME; BLM

Clinical Synopsis

INHERITANCE :

Autosomal recessive

GROWTH :

Height

Average adult male height 151cm

Average adult female height 144cm

Other

Prenatal onset growth retardation

Growth failure

HEAD AND NECK :

Head

Dolichocephaly

Microcephaly

Face

Narrow

Malar hypoplasia

Ears

Prominent ears

Nose

Prominent nose

Teeth

Absent upper lateral incisors

RESPIRATORY :

Airways

Bronchiectasis

Lung

Chronic lung disease

GENITOURINARY :

Internal genitalia, male

Azoospermia

Cryptorchidism

Internal genitalia, female

Reduced fertility in females

SKELETAL :

Hands



Syndactyly
Polydactyly
Fifth finger clinodactyly

SKIN, NAILS, HAIR :

Facial telangiectasia in butterfly midface distribution (exacerbated by sun)
Spotty hypopigmentation
Spotty hyperpigmentation
Cafe-au-lait spots
Hypertrichosis
Photosensitivity



NEUROLOGIC :

Central nervous system
Mild mental retardation in some
Learning disability

VOICE :

High-pitched

ENDOCRINE FEATURES :

Noninsulin-dependent diabetes mellitus

IMMUNOLOGY :

Immunoglobulin deficiency (IgA, IgG, IgM)
Impaired lymphocyte proliferation response to malignancy

NEOPLASIA :

Leukemia
Lymphoma
Adenocarcinoma
Squamous cell carcinoma
Hypersensitivity to chemotherapy

LABORATORY ABNORMALITIES :

High sister chromatid exchange (SCE) rate
SCE normal in heterozygotes
Increased chromosomal breakage
Decreased IgA, IgG, IgM

MISCELLANEOUS :

Life-threatening infections
Predisposition to neoplasia

MOLECULAR BASIS

Caused by mutations in the RecQ protein-like 3 gene (RECQL3, [604610.0001](#))



CHARGE Association / OMIM2008

HALL-HITTNER SYNDROME; HHS

Clinical Synopsis

INHERITANCE :

Autosomal dominant. Isolated cases. Caused by mutation in the chromodomain helicase DNA-binding protein 7 gene (CHD7, [608892.0001](#))



GROWTH :

Postnatal growth retardation



HEAD AND NECK :

Head

Microcephaly



Face

Square face

Malar flattening

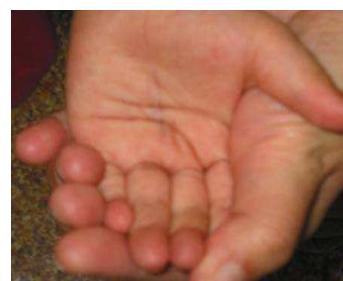
Micrognathia

Facial

asymmetry

Ears

Small ears



Lop ears

Deafness (sensorineural or mixed sensorineural and conductive)



Mondini defect

Eyes



Colobomas (iris, choroid, retina, disk, and optic nerve)

Anophthalmia

Ptosis

Hypertelorism

Down-slanting palpebral fissures

Nose

Posterior choanal atresia (membranous and/or bony)

Mouth



Cleft palate

Cleft lip



CARDIOVASCULAR :

Heart

Tetralogy of Fallot

Atrial septal defect
Double-outlet right ventricle



CHEST :

Ribs, sternum, clavicles, and scapulae
Rib anomalies

ABDOMEN :

External features

Umbilical hernia

Omphalocele

Gastrointestinal

Tracheoesophageal fistula

Anal atresia

Anal stenosis

Poor feeding



GENITOURINARY :

Delayed pubertal development

External genitalia, male

Micropenis

External genitalia, female

Hypoplastic labia

Internal genitalia, male

Cryptorchidism

Kidneys

Horseshoe kidney

Hydronephrosis



NEUROLOGIC :

Central nervous system

Mental retardation

Peripheral nervous system

Facial palsy

Dysphagia



ENDOCRINE FEATURES :

Growth hormone deficiency

Parathyroid hypoplasia

MISCELLANEOUS :

CHARGE acronym (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness)

CRI-DU-CHAT / OMIM 2008

Clinical Synopsis

INHERITANCE :

Deletion of the short arm of chromosome 5

Most characteristic features in newborn is
a high-pitched cat-like cry



GROWTH :

Failure to thrive in infancy

HEAD AND NECK :

HEAD

Microcephaly



Face

Round face

Micrognathia

Ears

Low-set ears



SKELETAL :

Vertebral abnormalities

MUSCLE, SOFT TISSUE :

Hypotonia

NEUROLOGIC :

Mental retardation

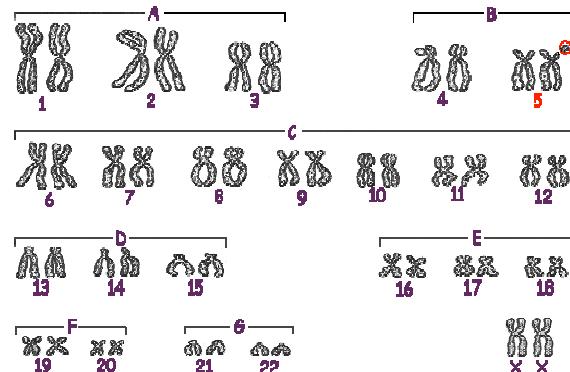
Behavioral/psychiatric manifestations

Severe psychomotor retardation

Destructive behavior, self mutilation, aggression

MISCELLANEOUS :

- One of the most common human deletion syndromes, incidence 1 in 20,000 to 1 in 50,000 births
- Deletions can vary in size from involving only band to all short arm
- Majority of deletions are new mutations
- 12% unbalanced translocations or recombination pericentric inversion in one of parents
- The majority die in early childhood
- With advancing age, the clinical manifestations become less striking(loss of hypertelorism and epicanthic folds, and development of a thin, narrow face with prominent nasal bridge) making diagnosis more difficult



MOLECULAR BASIS

High-pitched cry mapped to proximal 5p15.3 ([probe D5S727](#))
Remaining features of the syndrome mapped to 5p15.2 ([probe D5S721](#))
Deletions that did not include these 2 chromosomal regions presented varying clinical phenotypes from severe mental retardation and microcephaly to a clinically normal phenotype.

DIGEORGE SYNDROME; DGS CHROMOSOME 22q11.2 DELETION SYNDROME CATCH22 / OMIM 2008

Clinical Synopsis

INHERITANCE :

Autosomal dominant

GROWTH :

Height

Short stature (20% of adults)

Weight

Obesity (35% of adults)



HEAD AND NECK :

Face

Micrognathia

Ears

Low-set ears

Abnormal folded pinna

Middle ear abnormalities

Hearing deficits (28% of adults)

Eyes

Posterior embryotoxon

Tortuous retinal vasculature

Hypertelorism

Short palpebral fissures

Eyelid hooding

Amblyopia

Strabismus (15% of adults)

Exotropia

Esophoria

Accommodative esotropia

Complicated strabismus

Nose

Blunted nose

Short philtrum

Mouth

High arched palate



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Cleft palate

Bifid uvula

CARDIOVASCULAR :

Heart

Cardiovascular malformations (26% of adults)

Tetralogy of Fallot

Truncus arteriosus

Interrupted aortic arch

Right aortic arch

Ventricular septal defect

Vascular

Patent ductus arteriosus



ABDOMEN :

External features

Umbilical hernia

Femoral hernia

Biliary tract

Cholelithiasis (19% of adults)



GENITOURINARY :

External genitalia, male

Inguinal hernia

Kidney

Unilateral renal agenesis

Renal dysplasia

Hydronephrosis



SKELETAL :

Spine

Scoliosis (47% of adults)

SKIN, NAILS, HAIR :

Skin

Severe acne (23% of adults)

Seborrhea (35% of adults)



NEUROLOGIC :

Central nervous system

Mild to moderate learning difficulties

Delayed psychomotor development

Late-onset speech development

Tetany

Seizures (40%)

Behavioral/psychiatric manifestations

Attention deficit disorder
Schizophrenia (22% of adults)
Bipolar disorder

VOICE :

Hypernasal speech

ENDOCRINE FEATURES :

Parathyroid hypoplasia
Parathyroid absence
Thymic hypoplasia
Thymic aplasia
Accessory thyroid tissue
Hypothyroidism (20% of adults)



IMMUNOLOGY :

Immune defect due to a T cell deficit
Susceptibility to infection



LABORATORY ABNORMALITIES :

Neonatal hypocalcemia
Hypocalcemia (64% of adults)
T-cell deficit
85-90% DGS patients have deletion of 22q11.2
Other cytogenic abnormalities have been associated with DGS phenotype including monosomy 10p13, 11p13, and 4q21

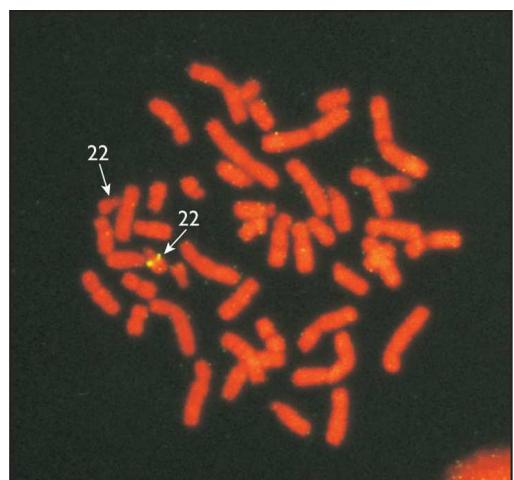


MISCELLANEOUS :

Incidence of approximately 1 in 5,000 live births
Hernia occurs in 22% of adults
Usually sporadic disorder resulting from de novo 22q11.2 deletion
22q11.2 deletion can present with a variety of phenotypes including velocardiofacial syndrome ([192430](#))

MOLECULAR BASIS

A contiguous gene syndrome involving deletion of the DiGeorge syndrome chromosome region (DGCR) involving mutations in TUP-like enhancer of split 1 (TUPLE1, [600237](#)) and DiGeorge critical region gene 2 (DGCR2, [600594](#))



DOWN SYNDROME

Clinical Synopsis

INHERITANCE :

Isolated cases

GROWTH :

Height

Short stature

HEAD AND NECK :

Head

Brachycephaly

Face

Flat facial profile

Ears

Small ears

Folded helix

Conductive hearing loss

Eyes

Upplanting palpebral fissures

Epicantal folds

Iris Brushfield spots

Mouth

Protruding tongue

CARDIOVASCULAR :

Heart

Congenital heart defect

Atrioventricular canal

ABDOMEN :

Gastrointestinal

Duodenal stenosis/atresia

Imperforate anus

Hirschsprung disease

SKELETAL :

Spine

Atlantoaxial instability

Pelvis

Hypoplastic iliac wings

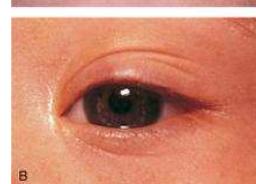
Shallow acetabulum



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A



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Limbs

Joint laxity

Hands

Short, broad hands

Fifth finger mid-phalanx hypoplasia

Single transverse palmar crease

SKIN, NAILS, HAIR :

Skin

Excess nuchal skin

Single transverse palmar crease



NEUROLOGIC :

Central nervous system

Mental retardation

Alzheimer disease

Hypotonia, poor Moro reflex



ENDOCRINE FEATURES :

Hypothyroidism

HEMATOLOGY :

Leukemoid reactions

NEOPLASIA :

Leukemia (both ALL and AML)

Acute megakaryocytic leukemia



MISCELLANEOUS :

Meiotic origin >95% maternal, mostly meiosis I

Increased recurrence risk with parental translocation

Incidence, 1 in 650-1000 live births

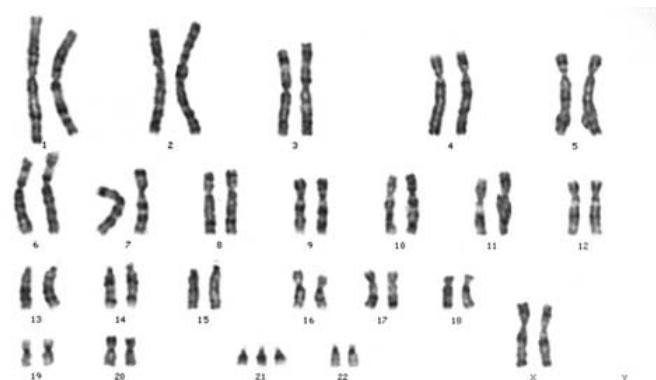


Down Syndrome newborn

MOLECULAR BASIS

Gene map locus [Xp11.23, 21q22.3, 1q43](#)

- Full trisomy 21, 94%
- Mosaic trisomy 21, 2.4%
- Translocation 21, 3.3%



FANCONI ANEMIA; FA

Clinical Synopsis

Growth :

- Low birth weight
- Small stature



Skel :

- Radial aplasia
- Thumb deformity
- Thumb aplasia
- Thumb hypoplasia
- Duplicated thumb



Heme :

- Anemia
- Neutropenia
- Thrombocytopenia
- Reticulocytopenia
- Pancytopenia
- Bleeding
- Leukemia



Skin :

- Anemic pallor
- Bruisability
- Pigmentary changes
- Hyperpigmentation
- Cafe-au-lait spots



HEENT :

- Microcephaly
- Strabismus
- Microphtalmia
- Ear anomaly
- Deafness

Cardiac :

- Congenital heart defect



GU :

- Kidney malformation
- Absent kidney

Duplicated kidney
Duplicated collecting system
Horseshoe kidney
Renal ectopia
Hypergonadotropic hypogonadism
Cryptorchidism

Neuro :

Mental retardation

Lab :

Multiple chromosomal breaks
Chromosomal breakage induced by diepoxybutane (DEB),
and mitomycin C
Deficient excision of UV-induced pyrimidine dimers in DNA
Prolonged G2 phase of cell cycle

Inheritance :

Autosomal recessive with at least two loci and possibly
multiple alleles



Clinical Synopsis

Gene map locus [16q24.3](#)



Fragile X syndrome / OMIM 2008

Clinical Synopsis

INHERITANCE :

X-linked dominant

HEAD AND NECK :

Head

Macrocephaly

Face

Coarse facial features

Large forehead

Long face

Prominent jaw

Ears

Large ears

CARDIOVASCULAR :

Heart

Mitral valve prolapse

Cardiovascular

Mild dilatation of ascending aorta

CHEST :

Ribs, sternum, clavicles, and scapulae

Pectus excavatum

GENITOURINARY :

External genitalia, male

Macroorchidism, postpubertal

Congenital macroorchidism (some cases)

SKELETAL :

Spine

Scoliosis

Limbs

Joint laxity

Feet

Pes planus

NEUROLOGIC :

Central nervous system

Mental retardation (moderate to severe in males)

Abnormal head movements



Behavioral/psychiatric manifestations

Hyperactive behavior

Poor eye contact

Autism

LABORATORY ABNORMALITIES :

Folate-dependent fragile site at Xq28

MISCELLANEOUS :

Incomplete penetrance

50% of females have learning disability or mild mental retardation

Prevalence approximately 1 in 4,000 males

Most cases (98%) caused by expanded trinucleotide repeat (CGG) n in the FMR1 gene

Repeat is unstable if > 52 repeats

Symptomatic if > 200 repeats



MOLECULAR BASIS

Caused by mutation in the FMR1 gene ([309550.0004](#))



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JOUBERT SYNDROME; JBTS / OMIM 2008

CEREBELLOOCULORENAL SYNDROME

Clinical Synopsis

INHERITANCE :

Autosomal recessive

HEAD AND NECK :

Head

Macrocephaly

Face

Prominent forehead

High, rounded eyebrows

Hemifacial spasms

Ears

Low-set ears

'Tilted' ears

Eyes

Abnormal, jerky eye movements

Impaired smooth pursuit

Impaired saccades

Oculomotor apraxia

Coloboma of optic nerve

Chorioretinal coloboma

Retinal dysplasia (less common)

Retinal dystrophy (less common)

Epicantal folds

Ptosis

Nose

Upturned nose

Anteverted nostrils

Mouth

Triangular-shaped open mouth

Protruding tongue

Rhythmic tongue movements

Soft tissue tumors of the tongue (less common)

RESPIRATORY :

Neonatal breathing dysregulation



Hyperpnea, episodic
Tachypnea, episodic
Central apnea

ABDOMEN :

Liver
Hepatic fibrosis (less common)



GENITOURINARY :

Kidneys
Renal cysts (less common)

SKELETAL :

Hands
Polydactyly, postaxial (less common)
Massing digital phalanges (less common)
Feet
Polydactyly, postaxial (less common)



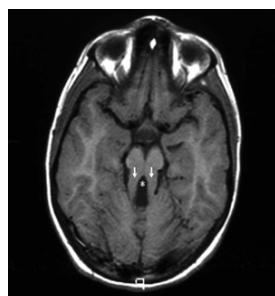
NEUROLOGIC :

Central nervous system
Delayed psychomotor development
Mental retardation
Ataxia
Hypotonia
Occipital meningocele (less common)
Occipital myelomeningocele (less common)
Hypoplasia of the brainstem
Malformation of brainstem structures
'Molar tooth sign' on MRI
Cerebellar vermis hypoplasia
Dysgenesis or agenesis of the cerebellar vermis
Deep posterior interpeduncular fossa
Thick and elongated superior cerebellar peduncles



Behavioral/psychiatric manifestations

Hyperactivity
Aggressiveness
Self-mutilation



MISCELLANEOUS :

Variable phenotype
Genetic heterogeneity (see JBTS2
[608091](#), JBTS3 [608629](#), JBTS4
[609583](#))



MARFAN SYNDROME; MFS / OMIM 2008

Clinical Synopsis

INHERITANCE :

Autosomal dominant

GROWTH :

Height

Mean length at birth 53 +/- 4.4 cm for males

Mean length at birth 52.5 +/- 3.5 cm for females

Mean adult height 191.3 +/- 9 cm for males

Mean adult height 175.4 +/- 8.2 cm for females

Disproportionate tall stature, upper to lower segment ratio less than 0.85

Arm span to height > 1.05

Other

Puberty-associated peak in growth velocity is 2.4 years earlier for males and 2.2 years earlier for females



HEAD AND NECK :

Head

Dolichocephaly

Face

Long, narrow face

Malar hypoplasia

Micrognathia

Retrognathia

Eyes

Enophthalmos

Ectopia lentis

Myopia

Increased axial globe length

Corneal flatness

Retinal detachment

Iris hypoplasia

Early glaucoma

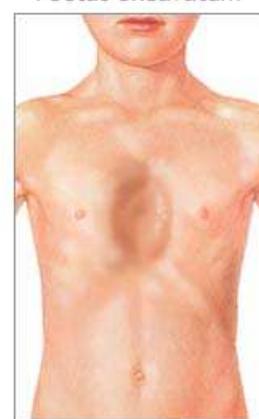
Early cataracts

Down-slanting palpebral fissures

Mouth

High-arched palate

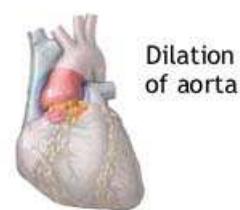
Pectus excavatum



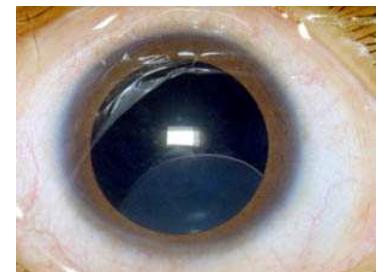
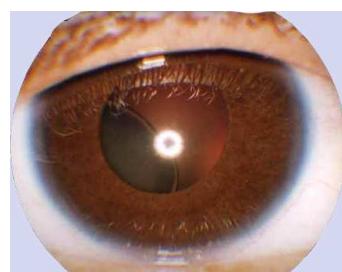
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Dilation of aorta



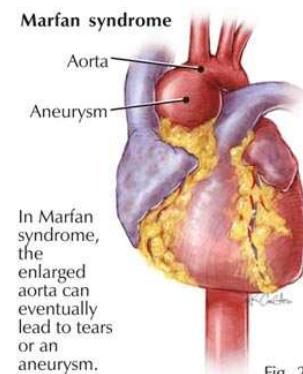
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- Narrow palate
 - Teeth
 - Crowded teeth
- CARDIOVASCULAR :**
- Heart
 - Aortic regurgitation
 - Mitral regurgitation
 - Mitral valve prolapse
 - Congestive heart failure
 - Tricuspid valve prolapse
 - Premature calcification of mitral annulus



- Vascular
 - Aortic root dilatation
 - Aortic dissection
 - Ascending aortic aneurysm
 - Aneurysm of other aortic segments rare
 - Pulmonary artery dilatation



RESPIRATORY :

- Lung
 - Emphysema in most severe presentation
 - Pneumothorax
 - Pulmonary blebs

CHEST :

- Ribs, sternum, clavicles, and scapulae
 - Pectus excavatum
 - Pectus carinatum
 - Pectus asymmetric sternum



ABDOMEN :

- External features
 - Recurrent or incisional hernia

SKELETAL :

- Premature arthritis
- Spine
 - Scoliosis
 - Kyphoscoliosis
 - Thoracic lordosis
 - Spondylolisthesis
 - Lumbosacral dural ectasia
- Pelvis
 - Protrusio acetabulae



Limbs

Long bone overgrowth (dolichostenomelia)

Joint hypermobility

Joint contractures

Genu recurvatum

Hands

Arachnodactyly

Feet

Pes planus

Long, narrow feet

Pes cavus

Hammer toes

Medial rotation of the medial malleolus

MUSCLE :

Decreased muscle mass

SKIN, NAILS, HAIR :

Skin

Striae distensae

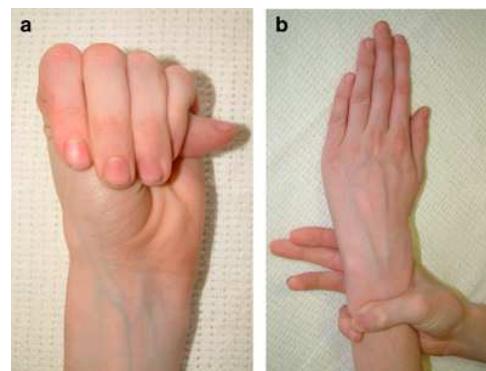
Decreased subcutaneous fat

LABORATORY ABNORMALITIES :

Decreased fibrillin-1 immunostaining in the dermis

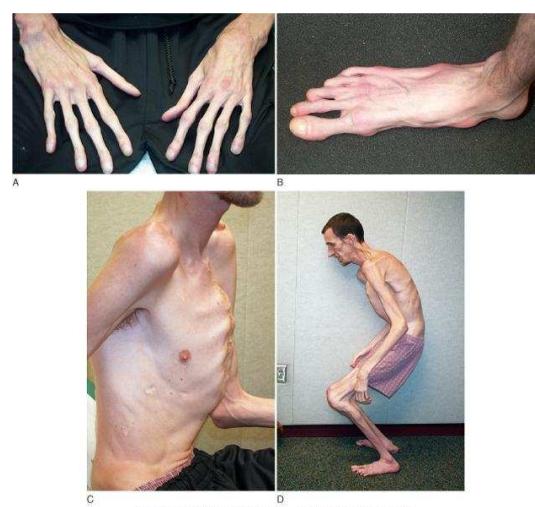
MISCELLANEOUS :

About 25% of cases due to new mutations



MOLECULAR BASIS

Caused by mutations in the fibrillin-1 gene ([FBN1, 134797.0001](#))



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NEUROFIBROMATOSIS, TYPE I; NF1 / OMIM2008

VON RECKLINGHAUSEN DISEASE

Clinical Synopsis

INHERITANCE :

Autosomal dominant

HEAD AND NECK :

Head

Macrocephaly , Sphenoid dysplasia



Eyes

Lisch nodules (iris hamartomas)

Glaucoma

Hypertelorism



CARDIOVASCULAR :

Vascular

Renal artery stenosis

Hypertension

SKELETAL :

Spine

Scoliosis

Spina bifida

Limbs

Pseudoarthrosis

Thinning of long bone cortex

Local bony overgrowth



SKIN, NAILS, HAIR :

Skin

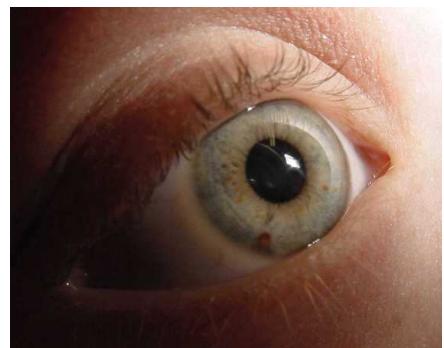
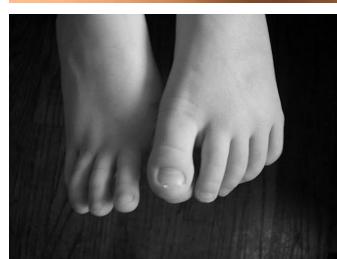
Neurofibromas

Plexiform neurofibroma

Cafe-au-lait spots

Axillary freckling

Inguinal freckling



NEUROLOGIC :

Central nervous system

Mental retardation, 30% learning disabilities, 10%

mild mental retardation

Aqueductal stenosis

Hydrocephalus

NEOPLASIA :

- Optic glioma
- Meningioma
- Hypothalamic tumor
- Neurofibrosarcoma
- Rhabdomyosarcoma
- Duodenal carcinoid
- Somatostatinoma
- Parathyroid adenoma
- Pheochromocytoma
- Pilocytic astrocytoma
- Malignant peripheral nerve sheath tumors



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Tumors at multiple other sites including CNS

MISCELLANEOUS :

50% of cases are caused by new mutations

MOLECULAR BASIS :

- Gene map locus [17q11.2](#)
- Caused by mutations in the neurofibromin gene (NF1, [162200.0001](#))



NOONAN SYNDROME 1; NS1 / OMIM 2008

Clinical Synopsis

INHERITANCE :

Autosomal dominant

GROWTH :

Height

Short stature (postnatal onset)

Other

Failure to thrive in infancy

Specific growth curves are available



HEAD AND NECK :

Face

Triangular face with age

Ears

Low-set posteriorly rotated ears

Nerve deafness

Eyes

Ptosis

Hypertelorism

Down-slanting palpebral fissures



Epicantal folds

Myopia

Blue-green irides

Mouth

Deeply grooved philtrum

High peaks of upper lip

vermillion border

High arched palate

Micrognathia

Dental malocclusion

Neck

Low posterior hairline

Webbed neck

Cystic hygroma



CARDIOVASCULAR :

Heart

Congenital heart defect

Atrial septal defects
Ventricular septal defects
Pulmonic stenosis
Vascular
Patent ductus arteriosus



CHEST :

Ribs, sternum, clavicles, and scapulae
Shield chest
Pectus carinatum superiorly
Pectus excavatum inferiorly



GENITOURINARY :

Internal genitalia, male
Occasional hypogonadism
Cryptorchidism
Male infertility in individuals with bilateral cryptorchidism

SKELETAL :

Spine
Vertebral abnormalities
Limbs
Cubitus valgus
Clinodactyly
Brachydactyly
Blunt fingertips



SKIN, NAILS, HAIR :

Hair
Wooly-like consistency of hair



MUSCLE, SOFT TISSUE :

Lymphedema

NEUROLOGIC :

Central nervous system
Articulation difficulties
Mental retardation (25%)



HEMATOLOGY :

Amegakaryocytic thrombocytopenia
Von Willebrand disease
Bleeding tendency

NEOPLASIA :

Malignant schwannoma

LABORATORY ABNORMALITIES :

Partial deficiency of factor XI:C

Partial deficiency of factor XII:C

Partial deficiency of factor XIII:C

Thrombocytopenia

MISCELLANEOUS :

Genetic heterogeneity (see NS2 [605275](#) and NS3 [609942](#))

Allelic with LEOPARD syndrome ([151100](#))



MOLECULAR BASIS

Caused by mutations in the protein tyrosine phosphatase, nonreceptor-type, 11 gene (PTPN11, [176876.0001](#))

PRADER-WILLI SYNDROME; PWS / OMIM2008

Clinical Synopsis

INHERITANCE :

Isolated cases

GROWTH :

Height

Normal birth length

Length deceleration in first few months

Mean adult male height, 155 cm

Mean adult female height, 147 cm

Steady childhood growth

Fall-off in adolescent growth

Weight

Failure to thrive in infancy

Onset of obesity from 6 months to 6 years

Central obesity



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HEAD AND NECK :

Head

Dolichocephaly

Face

Narrow bitemporal diameter

Eyes

Almond-shaped eyes

Strabismus

Upplanting palpebral fissures

Myopia

Hyperopia

Mouth

Thin upper lip

Small-appearing mouth

Down-turned corners of mouth

Thick, viscous saliva

Teeth

Early dental caries

RESPIRATORY :

Hypoventilation

Hypoxia

ABDOMEN :

Gastrointestinal

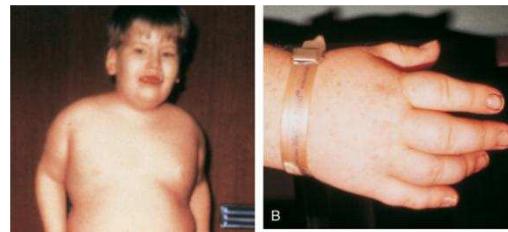
Feeding problems in infancy requiring gavage feeds
Decreased vomiting



GENITOURINARY :

External genitalia, male

Hypogonadotropic hypogonadism
Small penis
Scrotal hypoplasia



External genitalia, female

Hypoplastic labia minora
Hypoplastic clitoris



Internal genitalia, male

Cryptorchidism

Internal genitalia, female

Amenorrhea

Oligomenorrhea

SKELETAL :

Osteoporosis

Osteopenia

Spine

Scoliosis

Kyphosis

Hands

Small hands (<25th percentile for height age)

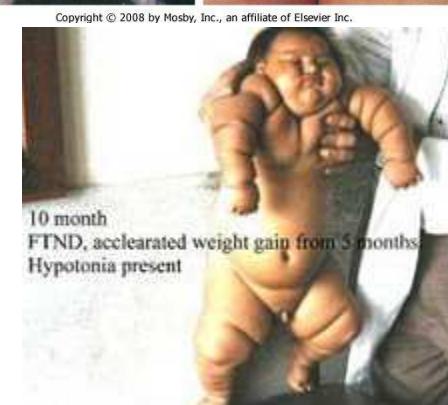
Narrow hands with straight ulnar border

Clinodactyly

Syndactyly

Feet

Small feet (<10th percentile for height age)



SKIN, NAILS, HAIR :

Hypopigmentation

Skin

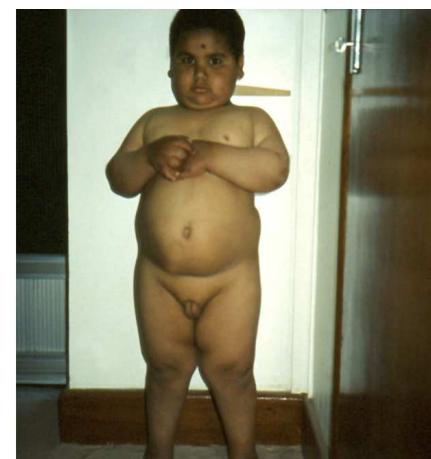
Fair skin

Sun sensitivity

Hair

Blonde to light brown hair

Frontal hair upsweep



NEUROLOGIC :

Central nervous system

- Mild-to-moderate mental retardation (~90%)
- Learning disabilities
- Severe neonatal hypotonia improving with age
- Normal neuromuscular studies
- Seizures
- Poor gross motor coordination
- Poor fine motor coordination
- Global developmental delay
- Behavioral problems
- Sleep disturbances
- High pain threshold
- Poor neonatal suck and swallow reflexes
- Speech articulation problems
- Childhood polyphagia



VOICE :

- Hypernasal speech
- Weak or squeaky cry in infancy

ENDOCRINE FEATURES :

- Hyperinsulinemia
- Growth hormone deficiency
- Hypogonadotropic hypogonadism



MISCELLANEOUS :

- Excessive skin picking of sores
- Food related behavioral problems include excessive appetite and obsession with eating
- Temperature instability
- High pain threshold
- Decreased fetal activity
- Breech position
- Behavioral problems including stubbornness and rage
- Sleep disturbance or sleep apnea (obstructive, central, or mixed)
- Unusual skill with jigsaw puzzle

MOLECULAR BASIS

Microdeletion of 15q11 in 70% of patients confirmed by fluorescent in situ hybridization

Remainder of cases secondary to maternal disomy

Rare cases secondary to chromosome translocation

HUTCHINSON-GILFORD PROGERIA SYNDROME; HGPS / *OMIM2008*

Clinical Synopsis

INHERITANCE :

Autosomal dominant

GROWTH :

Other

Postnatal onset growth retardation

HEAD AND NECK :

Face

Midface hypoplasia

Micrognathia



CARDIOVASCULAR :

Cardiac

Premature atherosclerosis

Premature coronary artery disease

Angina pectoris

Myocardial infarction

Congestive heart failure



SKELETAL :

Generalized osteoporosis with pathologic fractures



Progeria: Premature aging. Usually die at 10-15 yrs. of heart failure.
SS Gellis, M Feingold. Atlas of Mental Retardation Syndromes. 1968.

SKIN, NAILS, HAIR :

Skin: Absence of subcutaneous fat

Hair: Alopecia

MISCELLANEOUS :

Probably autosomal dominant with rare instances of affected sibs due to germinal mosaicism

Premature aging

Median life expectancy, 13.4 years

Paternal age effect



MOLECULAR BASIS

Gene map locus [1q21.2](#)

Caused by mutation in the lamin A/C gene (LMNA,
[150330.0022](#))

RETT SYNDROME; RTT / OMIM2008

Clinical Synopsis

INHERITANCE :

X-linked dominant

GROWTH :

Height

Short stature

Weight

Cachexia



HEAD AND NECK :

Head

Normal birth head circumference



Deceleration of head growth

Microcephaly

Teeth

Bruxism

CARDIOVASCULAR :

Heart

Prolonged QTc interval

T-wave abnormalities



RESPIRATORY :

Periodic apnea while awake

Intermittent hyperventilation

Breath holding

ABDOMEN :

Gastrointestinal

Constipation

Gastroesophageal reflux

SKELETAL :

Spine

Scoliosis

Kyphosis

Feet

Small feet

Cold feet

Vasomotor disturbance



MUSCLE :

Muscle wasting



NEUROLOGIC :

Central nervous system

Normal development until 6-18 months

Mental retardation, profound

Spasticity

EEG abnormalities - slow waking background, intermittent rhythmical slowing (3-5Hz), epileptiform discharges

Seizures

Reduction or loss of acquired skills (e.g., purposeful hand use, speech)

Gait ataxia

Gait apraxia

Truncal ataxia

Dystonia

Cortical atrophy (frontal area)



Behavioral/psychiatric manifestations

Autistic behaviors

Hand stereotypies (e.g., hand wringing)

Sleep disturbance

Bruxism

Breath holding



MISCELLANEOUS :

Prevalence 1/10,000-1/15,000 female births

Initially normal for first 6-18 months which is then followed by withdrawal and regression

Four clinical stages - Stage I, early onset stagnation (onset 6 months-1.5 year)

Stage II, rapid developmental regression (onset 1-4 years)

Stage III, pseudostationary period (onset 2-10 years)

Stage IV, late motor deterioration (when ambulation ceases)

Most cases are sporadic

De novo mutations occur almost exclusively on the paternally derived X chromosome



MOLECULAR BASIS

Caused by mutations in the methyl-CpG-binding protein-2 gene (MECP2, [300005.0001](#))

SANJAD-SAKATI SYNDROME/ OMIM 2008 HYPOPARATHYROIDISM-RETARDATION-DYSMORPHISM SYNDROME; HRD

Clinical Synopsis

INHERITANCE :

Autosomal recessive

GROWTH :

Other

Severe intrauterine growth retardation

Postnatal growth retardation

HEAD AND NECK :

Head

Microcephaly

Face

Micrognathia

Prominent forehead

Long philtrum

Ears

Low-set ears

Posteriorly rotated ears

Eyes

Deep-set eyes

Nose

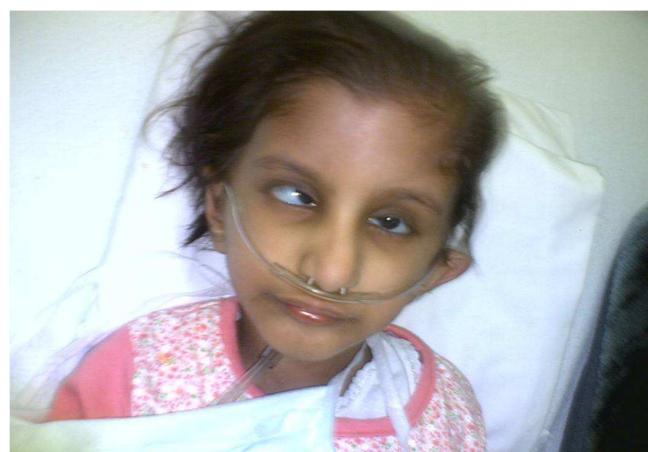
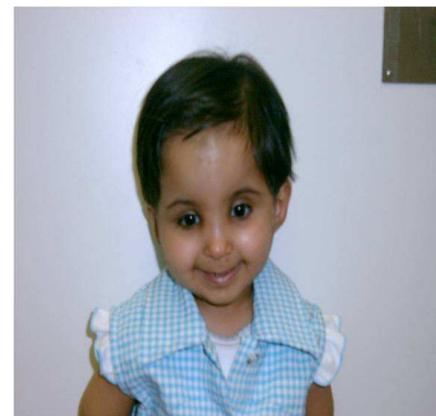
Beaked nose

Depressed nasal bridge

Mouth

Thin lips

Bifid uvula



GENITOUREINARY :

External genitalia, male

Micropenis

Internal genitalia, male

Cryptorchidism

SKELETAL :

Delayed bone age

Patchy osteosclerosis

Hands

Small hands

Feet

Small feet

NEUROLOGIC :

Central nervous system

Tetany

Hypocalcemic seizures

Mental retardation

Mild-moderate ventricular dilatation

ENDOCRINE FEATURES :

Low parathyroid hormone

Congenital hypoparathyroidism

IMMUNOLOGY :

Normal cell mediated immunity

Recurrent bacterial infections

LABORATORY ABNORMALITIES :

Hypocalcemia

Hyperphosphatemia

MISCELLANEOUS :

Allelic with Kenny-Caffey syndrome type 2 ([244460](#))

MOLECULAR BASIS

Caused by mutation in the tubulin-specific chaperone E gene (TCBE,
[604934.0001](#))

Gene map locus [1q42-q43](#)

SILVER-RUSSELL SYNDROME; SRS

Clinical Synopsis

INHERITANCE :

Isolated cases

GROWTH :

Height

Average adult male height, 149.5 cm

Average female adult height, 138 cm

Weight

Small for gestational age infant

Other

Lateral asymmetry

Partial or total asymmetry

Intrauterine growth retardation



HEAD AND NECK :

Head

Pseudohydrocephalic appearance

Normal head circumference

Face

Small, triangular facies

Micrognathia

Frontal bossing



Eyes

Blue sclera in infancy

Mouth

Down turned corners of mouth



CARDIOVASCULAR :

Heart

Cardiac defects

GENITOUREINARY :

Ureters

Posterior urethral valves

Hypospadias

SKELETAL :

Skeletal maturation retardation

Skull

Craniofacial disproportion

Delayed fontanel closure

Limbs

Asymmetry of arms and/or legs

Hands

Fifth finger clinodactyly

Fifth digit middle or distal phalangeal

hypoplasia

Feet

Syndactyly of 2nd-3rd toes



SKIN, NAILS, HAIR :

Cafe-au-lait spots

NEUROLOGIC :

Central nervous system

Developmental delay

ENDOCRINE FEATURES :

Fasting hypoglycemia

Growth hormone deficiency in some individuals

NEOPLASIA :

Craniopharyngioma

Testicular seminoma

Wilms tumor

Hepatocellular carcinoma



MISCELLANEOUS :

Marked heterogeneity

Majority cases are sporadic

Chromosome rearrangements have been reported

Maternal uniparental disomy (UPD) reported in some cases

SMITH-LEMLI-OPITZ SYNDROME; SLOS / OMIM 2008

Clinical Synopsis

INHERITANCE :

Autosomal recessive

GROWTH :

Height

Short stature

Weight

Birth weight <2500gm

Other

Failure to thrive

HEAD AND NECK :

Head

Microcephaly

Face

Micrognathia

Bitemporal narrowing

Ears

Low-set ears

Posteriorly rotated ears

Eyes

Ptosis

Epicantal folds

Cataracts

Hypertelorism

Strabismus

Nose

Anteverted nares

Broad, flat nasal bridge

Mouth

Cleft palate

Hypoplastic tongue

Broad alveolar margins

Teeth

Large central front teeth

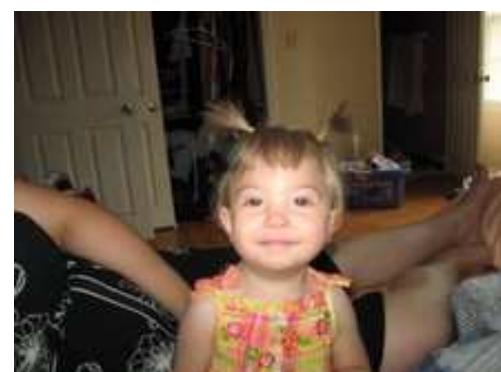
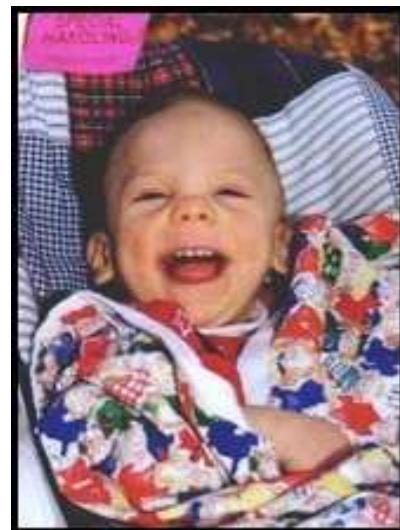
Dental crowding

CARDIOVASCULAR :

Heart

Ventricular septal defect

Atrial septal defect



Vascular

Coarctation of aorta
Patent ductus arteriosus

RESPIRATORY :

Lung

Hypoplastic lungs
Incomplete lobulation of the lungs

ABDOMEN :

Gastrointestinal

Poor suck
Vomiting
Constipation
Malrotation
Pyloric stenosis

GENITOURINARY :

External genitalia, male

Hypospadias
Ambiguous genitalia
Micropenis

Hypoplastic scrotum
Bifid scrotum
Microurethra

Internal genitalia, male

Cryptorchidism

Kidneys

Renal agenesis
Hydronephrosis
Single kidney
Cystic kidneys

Ureters

Ureteropelvic junction obstruction

SKELETAL :

Stippled epiphyses

Pelvis

Hip dislocation

Hip subluxation

Limbs

Limb shortening

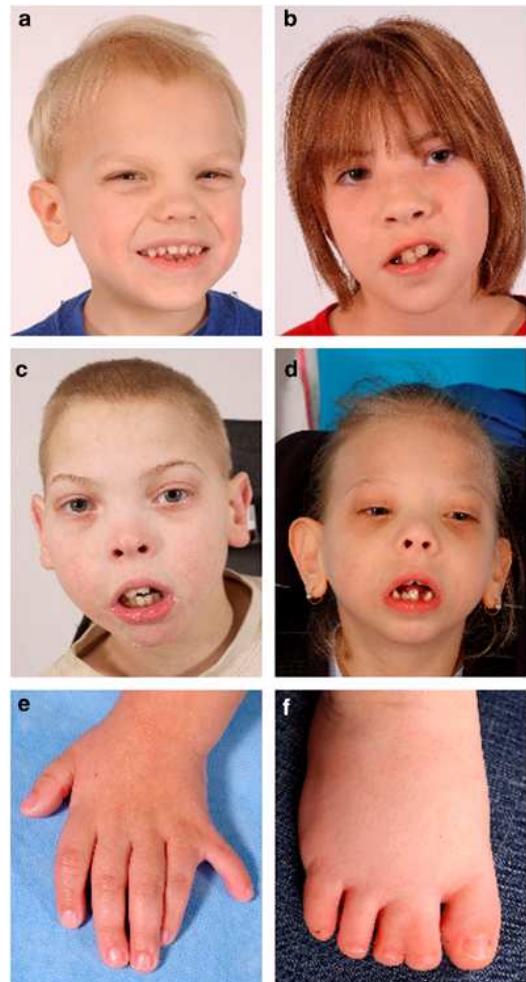
Hands

Short thumbs

Postaxial polydactyly

Proximally placed thumbs

Feet



Syndactyly of second and third toes

Postaxial polydactyly

Talipes calcaneovalgus

Short, broad toes

Overriding toes

Metatarsus adductus

SKIN, NAILS, HAIR :

Skin

Severe photosensitivity

Eczema

Facial capillary hemangioma

Hair

Blonde hair

NEUROLOGIC :

Central nervous system

Mental retardation

Seizures

Hypotonia (early infancy)

Hypertonia (childhood)

Hydrocephalus

Frontal lobe hypoplasia

Periventricular gray matter heterotopias

Abnormal sleep pattern

Behavioral/psychiatric manifestations

Self injurious behavior

Aggressive behavior

VOICE :

Shrill screaming

PRENATAL MANIFESTATIONS :

Movement

Decreased fetal movement

Delivery

Breech presentation

LABORATORY ABNORMALITIES :

Low cholesterol

Elevated 7-dehydrocholesterol

MISCELLANEOUS :

Estimated incidence 1/20,000 - 1/40,000



Figure 1 - Facial appearance of our confirmed cases of Smith-Lemli-Opitz syndrome (SLOS): (A) patient 1, (B) patient 2, (C) patient 3, (D) patient 4, (E) patient 5, (F) patient 6, (G) patient 7, (H) patient 8, (I) patient 9, (J) patient 10, (K) patient 11.



MOLECULAR BASIS

- Caused by mutations in the delta-7-dehydrocholesterol reductase gene (DHCR7, [602858.0001](#))
- Gene map locus [11q12-q13](#)

SOTOS SYNDROME / CEREBRAL GIGANTISM / OMIM2008

Clinical Synopsis

GROWTH :

Height

Mean full term birth length 55.2cm

Length at or greater than 97th percentile through early adolescence

Adult height often normal

Mean male adult height 184.3cm

Mean female adult height 172.9cm

Weight

Mean full term birth weight 3.9kg

Birth length often more increased than weight



HEAD AND NECK :

Head

Macrocephaly

Dolichocephaly

Face

Frontal bossing

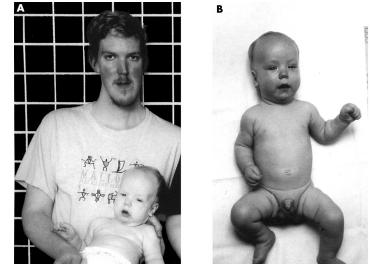
Prognathism

Pointed chin

Ears

Otitis media

Conductive hearing loss



Eyes

Downslanting palpebral fissures

Nystagmus

Strabismus

Hyperopia

Mouth

High arched palate

Teeth

Premature tooth eruption



CARDIOVASCULAR :

Heart

Atrial septal defect

Ventricular septal defect

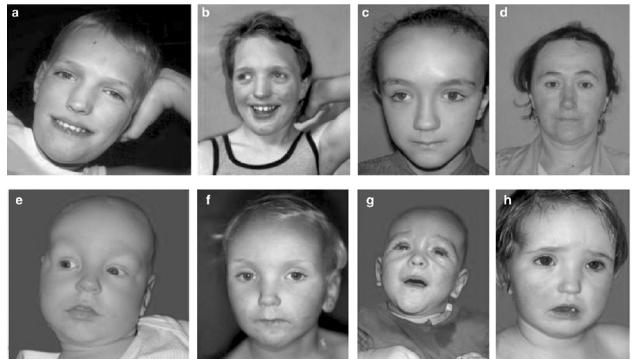
Vascular

Patent ductus arteriosus



SKELETAL :

- Advanced bone age
- Limbs**
- Joint laxity
- Genu valgus
- Long arm span
- Hands**
- Large hands
- Disharmonic maturation of phalanges and carpal bones
- Feet**
- Pes planus, Large feet



SKIN, NAILS, HAIR :

- Nails**
- Thin brittle fingernails
- Hair**
- Sparse hair in frontoparietal area



NEUROLOGIC :

- Central nervous system**
- Developmental delay
- Variable mental retardation
- Neonatal hypotonia
- Hyperreflexia
- Poor coordination
- Seizures
- Behavioral problems
- Expressive language delay
- Partial to complete agenesis of corpus callosum
- Persistent cavum septum pellucidum
- Large cisterna magna
- Ventriculomegaly , Prominent trigone and occipital horns



MISCELLANEOUS :

- Majority of cases are sporadic . Few familial (parent offspring) cases reported
- Slight increased risk for malignancy; Wilms tumor

MOLECULAR BASIS

- Gene map locus [5q35](#)
- Mutation in the nuclear receptor binding SET domain protein 1 gene (NSD1, [606681.0001](#))



VATER (VACTERL) association / OMIM 2008

Clinical Synopsis

INHERITANCE :

Isolated cases

GROWTH :

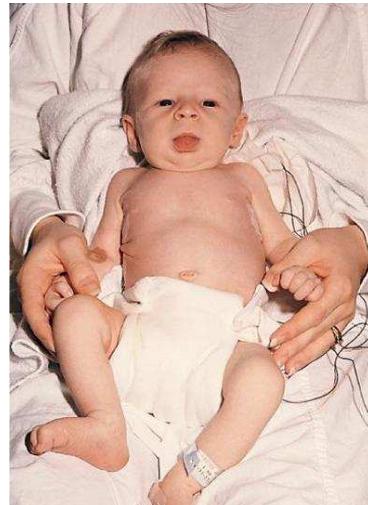
Weight

Failure to thrive

Other

Prenatal growth deficiency

Postnatal growth deficiency



HEAD AND NECK :

Head

Large fontanels

CARDIOVASCULAR :

Heart

Ventricular septal defects

Tetralogy of Fallot

Transposition of the great arteries

Vascular

Patent ductus arteriosus

RESPIRATORY :

Nasopharynx

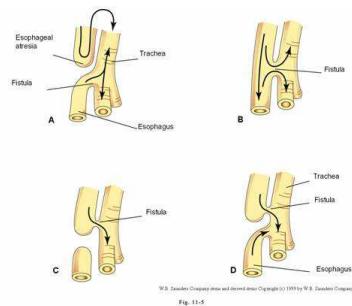
Choanal atresia

Larynx

Laryngeal stenosis

Airways

Tracheal agenesis

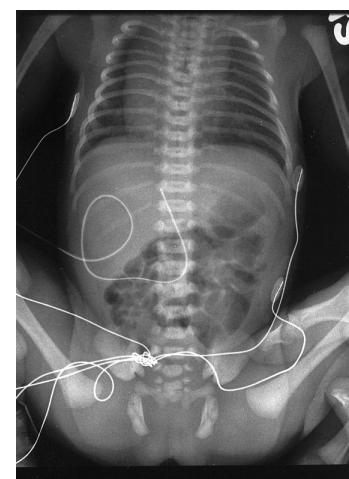
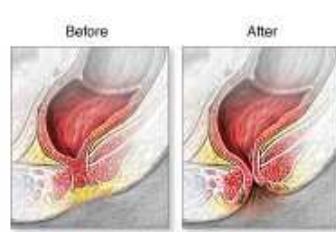


CHEST :

Ribs, sternum, clavicles, and scapulae

Rib anomalies

Sternal anomalies



ABDOMEN :

Gastrointestinal

Tracheoesophageal fistula

Esophageal atresia

Anal atresia

GENITOURINARY :

External genitalia, male

Hypospadias
Kidneys
Renal aplasia
Renal dysplasia
Hydronephrosis
Renal ectopia
Ureters
Vesicoureteral reflux
Ureteropelvic junction obstruction



Bladder
Persistent urachus

SKELETAL :

Spine
Vertebral anomalies
Scoliosis
Limbs
Radial aplasia
Radial hypoplasia
Radioulnar synostosis



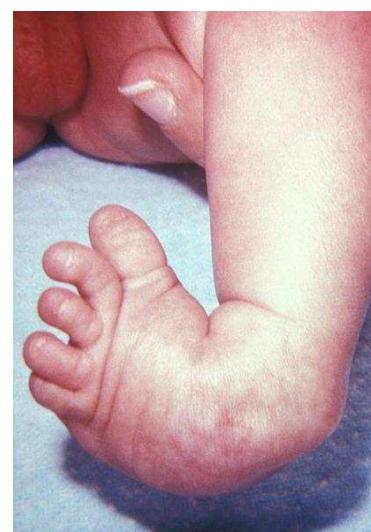
Hands
Thumb hypoplasia
Preaxial polydactyly
Syndactyly
Triphalangeal thumb



NEUROLOGIC :

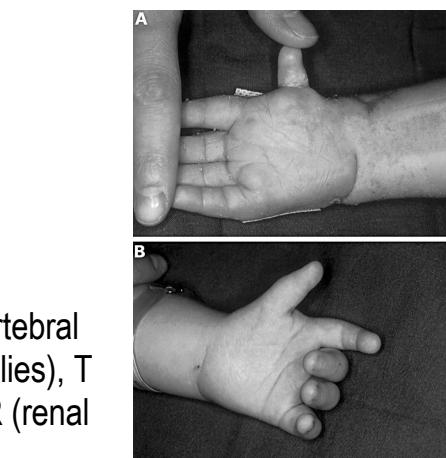
Central nervous system

Tethered cord
Spinal dysraphia
Occipital encephalocele



MISCELLANEOUS :

Single umbilical artery
Seen more frequently in infants of diabetic mothers
Estimated frequency 1.6 cases/10,000 live births
Nonrandom association of following anomalies--V (vertebral anomalies), A (anal atresia), C (cardiovascular anomalies), T (tracheoesophageal fistula), E (esophageal atresia), R (renal anomalies), L (preaxial limb anomalies)
Diagnosis made if 3/7 defects are present



WILLIAMS-BEUREN SYNDROME; WBS/ OMIM 2008

WILLIAMS SYNDROME

Clinical Synopsis

INHERITANCE :

Autosomal dominant

GROWTH :

Short stature

Other

Intrauterine growth retardation

HEAD AND NECK :

Face

Medial eyebrow flare

Flat midface

Periorbital fullness (puffy eyes)

Epicantal folds

Long philtrum

Ears

Sensorineural hearing loss, mild to moderate

Hyperacusis

Phonophobia

Abnormal brain auditory evoked responses (BAER)

Decreased or absent ipsilateral acoustic reflex response to maximum stimulation

Eyes

Stellate pattern of iris

Nose

Depressed nasal bridge

Anteverted nares

Mouth

Thick lips

Teeth

Hypodontia

Microdontia

CARDIOVASCULAR :

Heart

Supravalvular aortic stenosis

Valvular aortic stenosis



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Bicuspid aortic valve
Mitral valve prolapse
Mitral regurgitation
Coronary artery stenosis
Pulmonary valve stenosis
Atrial septal defect
Ventricular septal defect
Vascular
Peripheral pulmonary artery stenosis
Systemic hypertension

RESPIRATORY :



Larynx
Vocal cord paralysis

CHEST :

Ribs, sternum, clavicles, and scapulae
Pectus excavatum

ABDOMEN :

External features
Inguinal hernia
Gastrointestinal
Chronic constipation
Diverticulosis



GENITOURINARY :

Kidneys
Small kidneys
Solitary kidney
Pelvic kidney
Nephrocalcinosis
Renal insufficiency
Renal artery stenosis
Ureters
Vesicoureteral reflux
Bladder
Bladder diverticula
Urethral stenosis
Recurrent urinary tract infections



SKELETAL :

Spine
Kyphoscoliosis
Limbs



Joint limitation

Feet

Hallux valgus

NEUROLOGIC :

Central nervous system

Mental retardation (average IQ 56)

Relative sparing of language

Poor visual-motor integration (Range 41-80)

Hypersensitivity to sound

Behavioral/psychiatric manifestations

Attention deficit disorder

Cocktail party personality

Strong attraction to music



SKIN, NAILS, HAIR :

Nails

Hypoplastic nails



VOICE :

Harsh, brassy, or hoarse voice

ENDOCRINE FEATURES :

Hypercalcemia

LABORATORY ABNORMALITIES :

Hemizygous deletion at 7q11.23

MISCELLANEOUS :

Incidence 1 in 8,000 live births

Main aspects of phenotype attributed to defects in GTF2IRD1 ([604318](#)) and

GTF2I ([601679](#))

MOLECULAR

Contiguous gene syndrome involving mutation of genes on 7q11.2



WOLF-HIRSCHHORN SYNDROME; WHS / OMIM 2010

INHERITANCE:

Isolated cases

GROWTH:

Weight

Low birth weight

Other

Marked growth retardation

Failure to thrive

HEAD AND NECK:

Head

Microcephaly

Cranial asymmetry

Posterior midline scalp defects

Face

Prominent glabella

Short philtrum

Micrognathia

High forehead

Ears

Preauricular tags

Preauricular pits

Hearing loss

Narrow external auditory canals

Eyes

Strabismus

Hypertelorism

Epicantal folds

Exophthalmos

Ptosis

Rieger anomaly

Nystagmus

Iris coloboma

Corectopia

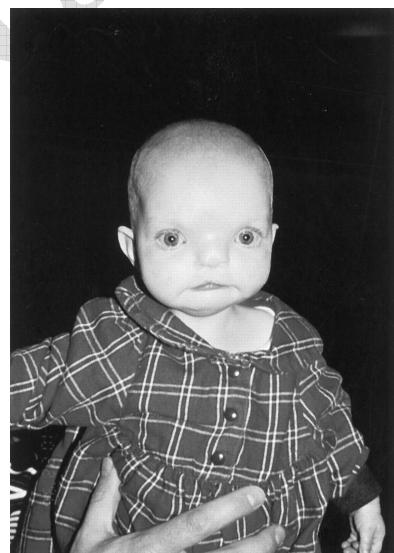
Nose

Wide nasal bridge

Beaked nose

Mouth

Cleft lip



Cleft palate

Downturned corners of mouth

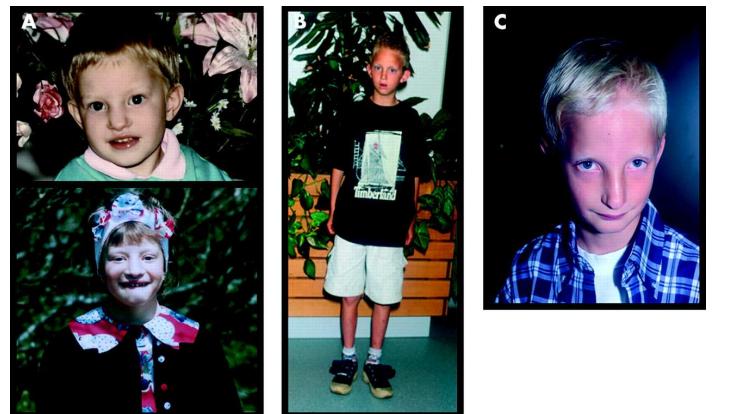
Short upper lip

Teeth

Hypodontia

Neck

Webbed neck



CARDIOVASCULAR:

Atrial septal defect

Ventricular septal defect

CHEST:

Ribs, sternum, clavicles, and scapulae

Sternal ossification center abnormalities

Fused ribs

ABDOMEN:

Absence of gallbladder

Accessory spleen

Malrotation of small bowel

Gastroesophageal reflux

GENITOURINARY:

External genitalia, male

Hypospadias

Internal genitalia, male

Cryptorchidism

Internal genitalia, female

Absent uterus



SKELETAL:

Delayed bone age

Spine

Sacral dimple

Sacral sinus

Scoliosis

Kyphosis

Fused vertebrae

Bifid vertebrae

Pelvis

Hip dislocation

Absence of pubic rami

Limbs

Thin limbs

Radioulnar synostosis

Hands

Transverse palmar creases

Accessory proximal metacarpal ossification centers

Feet

Talipes equinovarus

Metatarsus adductus

Polydactyly

SKIN, NAILS, HAIR:

Posterior midline scalp defects

Sacral dimple

Transverse palmar creases

Hyperconvex fingernails

Low posterior hairline

High-arched eyebrows

Sparse medial eyebrows



NEUROLOGIC:

Severe mental retardation

Hypotonia

Seizures

Cavum septum pellucidum

Absent septum pellucidum

Interventricular cysts

Hydrocephalus



ENDOCRINE FEATURES:

Precocious puberty

PRENATAL MANIFESTATIONS:

Decreased fetal activity

MISCELLANEOUS:

Sex ratio 2 females to 1 male

Partial deletion of short arm of chromosome 4.

De novo deletions in 8% of patients (preferentially paternally derived). 13% of cases secondary to familial translocation (often maternally derived). Size of deletion varies from cytogenetically visible deletions to undetectable cytogenetic deletions

FISH can be used to detect deletions of 4p16.3, the critical region for the phenotype. Approximately 35% of patients die during the first 2 years of life



MOSTAFA ELBABA