

THE DIFFERENTIAL DIAGNOSIS OF FETAL ALCOHOL SPECTRUM DISORDER

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ABSTRACT

Fetal Alcohol Spectrum Disorder (FASD) affects an estimated 1% of all children born in North America. FASD is a chronic disorder impacting many systems of care. Only a minority of these children exhibit the pathognomonic facial features of Fetal alcohol syndrome (FAS) that include short palpebral fissures, smooth philtrum and thin upper lip. Hence, in the majority of affected individuals FASD is a diagnosis of exclusion. The differential diagnosis of both the dysmorphological and neurobehavioral aspects of FASD is wide. This review aims to provide the pediatrician with information concerning the differential diagnosis of FASD and to discuss genetic testing that might be relevant to the assessment.

Key Words: *FASD, differential diagnosis, pregnancy, ADHD, genetics*

Fetal Alcohol Spectrum Disorder (FASD) affects an estimated 1% of all children born in North America.¹ About 10% of these individuals exhibit the pathognomonic facial features (short palpebral fissures, smooth philtrum and thin upper lip) (Figure 1). There is also a wide range of minor anomalies and malformations that can result from PAE.¹ Hence in most affected individuals FASD is a diagnosis of exclusion.

The differential diagnosis of both the dysmorphology and neurobehavior of FASD is wide. Although a variety of references present short tables of differential diagnosis (d.d.) of FASD, these are invariably presented in the form of syndrome names, which does not permit a pediatrician who may not be trained in dysmorphology a straight forward use of this limited information.

There is also the concern of co-morbidity. Children with other genetic disorders or genetic syndromes associated with developmental delays or intellectual disabilities may also have had prenatal alcohol exposure (PAE). In most cases in which the genetic disorder has been confirmed by a clinical geneticist, it would be virtually impossible to determine if the individual meets

the diagnostic criteria for FASD, particularly in the absence of a biomarker of effect specific to FASD. In these cases, the disability predicted by the genetic disorder or syndrome will likely mask the effects of PAE.

Genetic testing is relevant to the diagnostic process for possible FASD in children who present with anomalies or are dysmorphic. Clinical geneticists are trained in dysmorphology, and pediatricians should involve geneticists in consultation in any child that is considered dysmorphic, whether or not PAE has been confirmed. A recent review of a genetics clinic experience in Manchester, England determined that of 80 children referred for FAS assessment only 20% were confirmed to have a FAS diagnosis.² The most common alternate diagnosis was a chromosome anomaly (8.75%). Therefore a genetic assessment was of particular value in excluding other diagnoses and providing accurate information to care givers.

In another study from Amsterdam, 27 children were evaluated in a genetics clinic for possible FAS.³ Two were identified to have a pathogenic microstructural chromosomal rearrangement. The authors cautioned that 22 of the children had other factors that may have

affected their intellectual abilities such as familial intellectual disability and social deprivation.

In those children with a suspected genetic disorder select genetic testing to confirm a diagnosis is appropriate. In those children who do not present with a bonafide known genetic syndrome, a chromosome microarray analysis is indicated. In non-dysmorphic children referred for FASD evaluation, in which there has been significant PAE and in which there is no obvious explanation in the family or the child for their

disability, genetic investigations probably have a limited value.

The primary objective of this review is to present the d.d. of FASD in an user- friendly manner. The data are summarized in two forms: Alphabetically (pages 4-26), and by clustering of existing features (page 27). After each entry there are abbreviated references. Full references are presented at the end pages 28-30.

FIG. 1 Facial changes in the full blown FAS

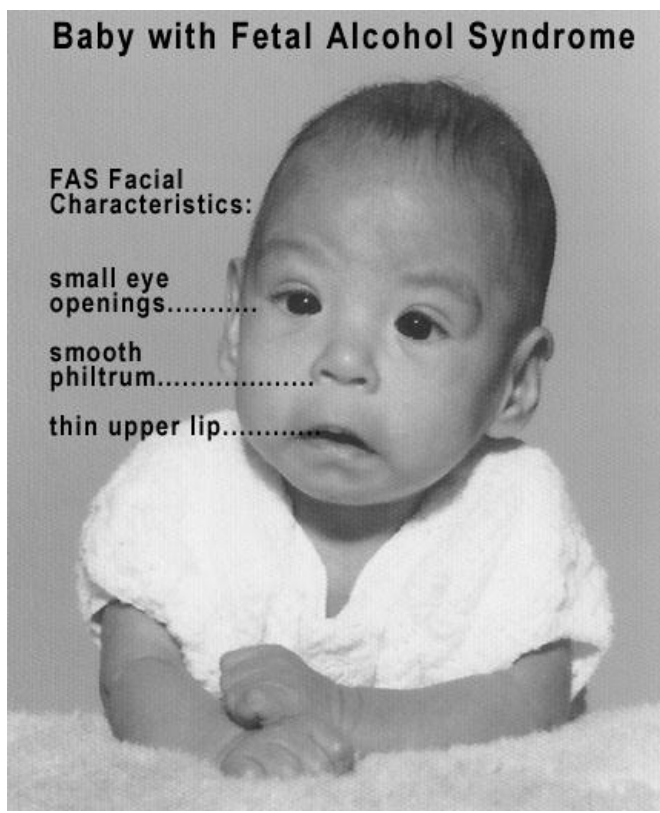


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Aarskog syndrome (AAS) (OMIM#305400)



Fryns, JP. The changing phenotype with age. American Journal of Medical Genetics 1992;43:420-427⁴

Clinical characteristics:

Males presenting with short stature associated with facial dysmorphism and genital anomalies. Key features include genital and musculoskeletal findings. Most have no intellectual impairment.

Genetic characteristics:

In most cases, inheritance is x-linked recessive and the implicated gene is FGD1, whose product is an essential guanine nucleotide exchange factor for GTP-binding proteins that are responsible for certain aspects of skeletal formation and morphogenesis.

Common features:

Midface (maxillary) hypoplasia, long and wide philtrum, ADHD with impulsive trait.

Distinctive features:

Facial: broad forehead, hypertelorism, normal palpebral fissures.

Other anomalies:

Shawl scrotum (scrotal folds encircling the base of the penis), short and broad hands and feet and hyperextension at the proximal interphalangeal joints.

Diagnostic testing:

Genetic testing for mutations (15 known) in FGD1 gene.

References

1. Optometry 2008;79:71-377.⁵
2. Arch Dis Child 1998;79:359-360.⁶

Bloom Syndrome (OMIM#210900)



Clinical characteristics:

The most common presentation is short stature with skin lesion and recurrent infections. As genomic instability is significant in these patients, presentation with malignancy at an early age is not uncommon.

Genetic characteristics:

This syndrome is a result of mutation in the BLM gene (located at 15q26.1), encoding for an important helicase protein designed to stabilize the DNA molecule during replication. Inheritance is autosomal recessive, with high carrier frequency in eastern European Jewish population.

Common features:

Midface hypoplasia, low attention span.

Distinctive features:

Facial: Narrow and long face, prominent nose and ears and [micrognathia](#).

Other anomalies:

Includes: telangiectatic skin lesions on sun exposed areas, café-au-lait spots, moderate immune deficiency with hypogammaglobulinemia and hypogonadism.

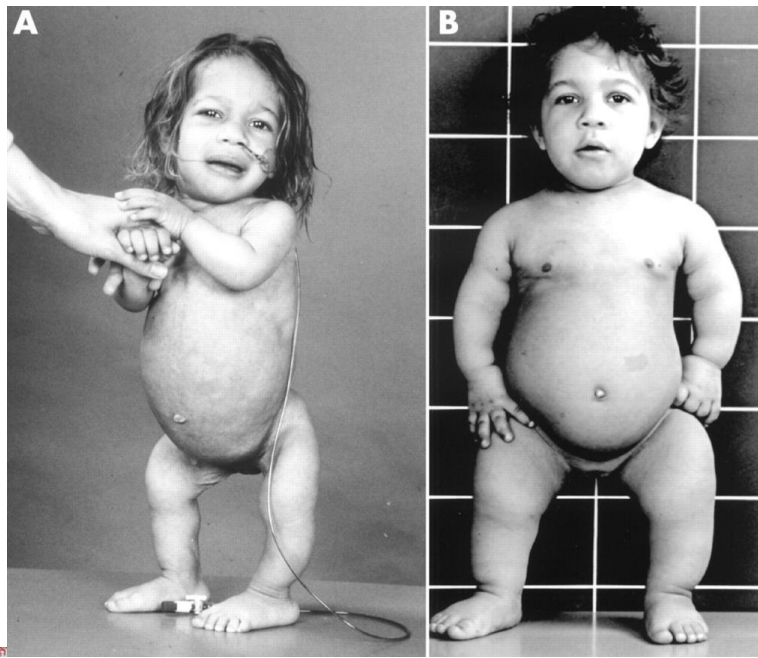
Diagnostic testing:

Genetic testing for four-arm chromatid interchange, high levels of sister-chromatid exchange or one of several known mutations in the BLM gene on chromosome 15.

References

1. Expert Rev Mol Diagn 2004;4(3):393-401.⁷
2. Clinical Genetics 1989;35:57-69.⁸

Campomelic dysplasia (OMIM #114290)



Clinical features:

Campomelic dysplasia is a syndrome affecting the development of the skeletal and reproductive systems. This includes hypotonia, short and bowed limbs, mainly lower, hypoplastic toes, prominent coccyx with overlying dimple. In addition, short neck, laryngotracheomalacia, small and bell shaped chest, and scoliosis are seen. Head and face deformities include dolichocephaly, large anterior fontanel, flat supraorbital ridges and bridge of nose, frontal upsweep of the anterior scalp hairline, small nose, anteverted nostrils, micrognathia and retrognathia, soft palate cleft, hypertelorism, short palpebral fissures, low set ears. Another important feature is ambiguous genitalia.

Genetic features:

May be inherited in an autosomal dominant manner. The mutation is in the SOX9 (SRY-box 9) gene, located on chromosome 17q23.

Common features:

Small palpebral fissures.

Distinctive features:

Stunning skeletal deformities, most patients succumb during infancy due to severe hypotony and respiratory failure.

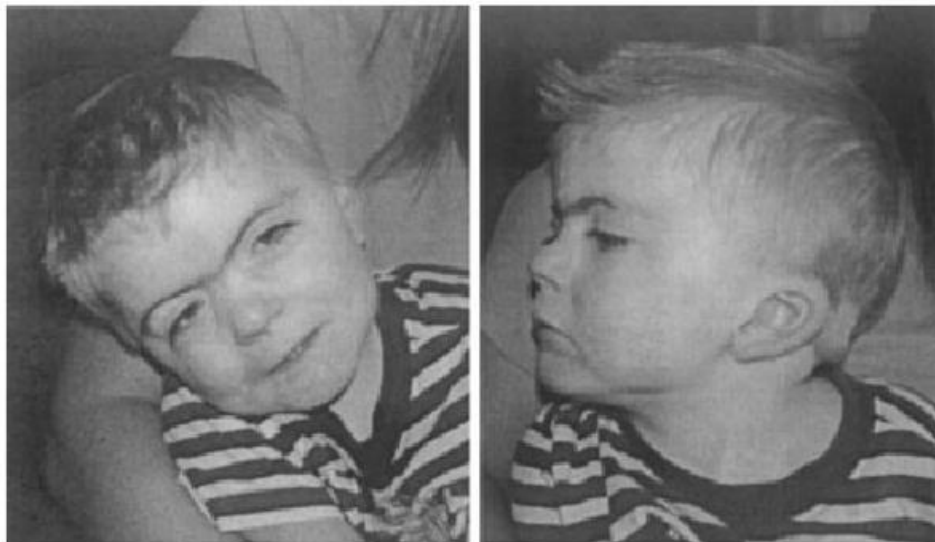
Diagnostic testing:

Clinical diagnosis, genetic testing.

References

1. American Journal of Medical Genetics 1983; 15:3-28.⁹
2. J Perinatol 2008;28:71.¹⁰
3. Eur J Hum Genet 2013 Jul;21:7.¹¹

Cornelia De-Lange syndrome (CDLS) (OMIM#122470) or Cornelia de Lange syndrome (CdLS; MIM #122470, 300590,610759, 300882, 614701)



Kaur M, et al. Am J Med Genet A 2005 September 15;138(1):27–31¹²
[doi:10.1002/ajmg.a.30919](https://doi.org/10.1002/ajmg.a.30919)

Clinical characteristics:

This multisystem autosomal dominant syndrome consists of characteristic facial features, growth retardation, microcephaly, neurologic disorders, hirsutism, abnormalities of the upper extremities, gastrointestinal problems, and a wide range of developmental delay.

Genetic characteristics:

Five genes have been implicated until now as causing this syndrome. The most common and first to have been recognized is NIPBL (MIM #608667), localized to chromosome 5p13. Mutations in this gene are found in at least 60% of patients. NIPBL and HDAC8 are both encoding for cohesin regulatory proteins, while the three other genes (SMC1A, SMC3, RAD21) encode core cohesin subunits. Disruption of the cohesin complex seems to interfere with sister chromatid cohesion and with gene regulation, although the exact relationship between the genotype and the phenotype has not been elucidated yet.

Common features:

Midface hypoplasia, long philtrum with thin upper lip, low IQ, hyperactivity.

Distinctive features:

Facial: fine arched eyebrows, synophrys, long eyelashes, low-set posteriorly rotated ears, depressed nasal bridge with anteverted nares, micrognathia, low posterior hairline, hirsute forehead and sometimes severe ptosis.

Other anomalies:

Seizures, heart defects, short neck, upper extremity defects ranging from small hands to severe malformations.

Diagnostic testing:

Genetic testing for mutations in any of the aforementioned genes.

References

1. Clin Genet 2009 October; 76(4):303–314.¹³
[doi:10.1111/j.1399-0004.2009.01271.x](https://doi.org/10.1111/j.1399-0004.2009.01271.x)
2. Pubmed Id 24038889.¹⁴

DiGeorge syndrome (DGS) (OMIM #188400)



www.myhealthyfeelings.com

Clinical characteristics:

Presentation is usually of a failing to thrive infant with history of recurrent infections. A further evaluation of such patients often reveals cardiac anomalies, immune deficiencies, palatal defects and cognitive impairment – all have high degree of variability and may only be diagnosed at a later stage.

Genetic characteristics:

De novo chromosome 22q11.2 deletions have been found to cause this syndrome. The most common one involves around 3Mb and the loss of 35 genes.

Common features:

Midface hypoplasia, Smooth philtrum, thin upper lip, ADHD.

Distinctive features:

Facial: hooded eyelid, bulbous nasal tip, nasal dimple, micrognathia, microtia, posteriorly rotated ears.

Other anomalies:

Congenital cardiac defects (TOF and VSD most common), T-cell lymphopenia, cleft palate, spinal abnormalities (c-spine instability most common), Postaxial polydactyly, and dental and renal structural anomalies.

Diagnostic testing:

Genetic testing - FISH study with chromosome 22-specific probes is the standard method for diagnosis. PCR-based diagnosis and use of SNP arrays are two alternatives that offer faster diagnosis and less likelihood to miss atypical deletions.

References

1. Chromosome 22q11.2 deletion syndrome review. *Medicine & Volume 90, Number 1, January 2011.*¹⁵

15q duplication syndrome (OMIM #608636)



Clinical features:

Hypotonia, downslanting or small palpebral fissures, epicanthal folds, deep-set eyes, low-set and/or posteriorly rotated ears, short philtrum, cleft or highly arched palate, broad nose, anteverted nares; 5th finger clinodactyly and unusual dermatoglyphics.

Other anomalies:

Includes cardiac, genitourinary, umbilical and inguinal hernias. Growth is retarded in about 20–30% of the patients. Microcephaly or macrocephaly may be present, as pubertal disorders. Neurological features include developmental delay/mental retardation, intractable epilepsy, autistic behavior (lack of social interaction, non-functional use of objects, primordial type of exploration, stereotypies, severe language delay, limited comprehension, and poor intention to communicate).

Genetic features:

Inheritance pattern is not known. The aberrancy is in the duplication of some parts of chromosome 15q, cytogenetically termed dic(15)(q12 or q13). If large enough region is involved, it may cause partial tetrasomy of 15q. Diagnostic testing is by FISH analysis.

Common features:

Small palpebral fissures, short philtrum, autistic behavior.

Distinctive features:

Intractable epilepsy.

Diagnostic testing:

Cytogenetic testing – FISH analysis.

References

1. Brain & Development 2005;27:365–369.¹⁶
2. Pediatr Neurol 2001 Feb;24(2):111-6.¹⁷

Dubowitz syndrome (OMIM #223370)



Clinical features:

Growth retardation, microcephaly, short stature, characteristic facial features, skin eruptions, and mild to severe mental retardation.[1]. Facial features include a triangular shaped face, sparse hair, sloping forehead, low set ear, sparse eyebrows and eyelash, blepharophimosis, small palpebral fissures, bilateral ptosis, epicanthus, broad and flat nasal bridge, micrognathia, and dental malocclusion. Behavioral characteristics include hyperactivity and short attention span, impulsivity and aggressiveness, shyness and a dislike of crowds, refusal of food and bedwetting. Decreased motor and language functioning, developmental delay, and mild to severe mental retardation. Systemic features include cardiovascular, gastrointestinal, urogenital, endocrinological, immunological, hematological, neurological, or musculoskeletal disorders.

Genetic features:

May be inherited in an autosomal recessive manner. The mutation is yet to be discovered.

Common features:

Small palpebral fissures, hyperactivity, short attention span, impulsivity and aggressiveness.

Distinctive features:

Eczema, autosomal dominant trait.

Diagnostic testing:

Clinical diagnosis.

References

1. Am J Med Genet 1996;63:277–289.¹⁸
2. Am J Med Genet 1980;6(1):3–8.¹⁹
3. J Clin Med Res 2011 August 3;(4):147–155.²⁰
4. American Journal of Medical Genetics January 1980;7(2):155-170.²¹

FG syndrome (Opitz–Kaveggia syndrome, OMIM #305450)



Clinical features:

Hypotonia, postnatal onset relative macrocephaly, prominent forehead, frontal hair upsweep or whorls, telecanthus or ocular hypertelorism, thin vermilion border of the upper lip, relatively short fingers with broad thumbs and halluces, persistent fetal fingertip pads, anal anomalies, and/or constipation. Major malformations are less common, and include pyloric stenosis, anal agenesis, cryptorchidism, hypospadias, and congenital heart defects. Epilepsy has been described. Neurocognitive features include developmental delay, hyperactivity, short attention span, affability, and excessive talkativeness.

Genetic features:

X-linked, recessive. MED12 gene, located on chromosome X, is involved. One mutation is p.Arg961Trp.

Common features:

Thin upper lip, hyperactivity.

Distinctive features:

Multiple congenital anomalies.

Diagnostic testing:

Cytogenetic testing – FISH analysis.

References

1. Am J Med Genet C Semin Med Genet 2010 Nov 15;154C(4):477-85.²²
2. Am J Med Genet A 2006 Oct 1;140(19):2075-9.²³

Floating harbor syndrome (FLHS) (OMIM#136140)



<http://www.brighthub.com/science/genetics/articles/93766.aspx>

Clinical characteristics:

Patients presenting with this rare genetic syndrome are usually diagnosed with a tetralogy of short stature, delayed bone age, delayed speech development, and typical facial features

Genetic characteristics:

Floating-Harbor syndrome is caused by heterozygous mutation in the SRCAP gene (611421) on chromosome 16p11.2.

Common features:

Smooth philtrum, thin upper lip.

Distinctive features:

Facial: triangular face with a prominent nose and deep-set eyes.

Other anomalies:

Short stature with delayed bone age and expressive language delay, genitourinary anomalies, celiac disease, congenital heart defects, and a high-pitched or nasal voice.

Diagnostic testing:

Genetic testing for mutations of the SRCAP gene on chromosome 16.

References

1. OMIM WEBSITE:
<http://omim.org/entry/136140>.²⁴
2. Am J Med Genet Part A 2010;152A:821–829.²⁵

Geleophysic dysplasia 1 (GPHYSD1) (OMIM #231050)



http://www.gfmer.ch/genetic_diseases_v2/gendis_detail_list.php?cat3=598

Clinical characteristics:

This rare syndrome is characterized by severe short stature, short hands and feet, joint limitations, and skin thickening.

Genetic characteristics:

Autosomal recessive disorder, caused by homozygous or compound heterozygous mutation in the ADAMTSL2 gene ([612277](#)) on chromosome 9q34.2.

Common features:

Long flat philtrum and a thin upper lip.

Distinctive features:

Facial: affected individuals have characteristic facial features including a 'happy' face with full cheeks, shortened nose and hypertelorism.

Other anomalies:

Musculoskeletal manifestations include delayed bone age, cone-shaped epiphyses, shortened long tubular bones, and ovoid vertebral bodies. Several life threatening problems described in this syndrome are: progressive cardiac valvular thickening, tracheal stenosis, respiratory insufficiency and lysosomal-like storage vacuoles in various tissues

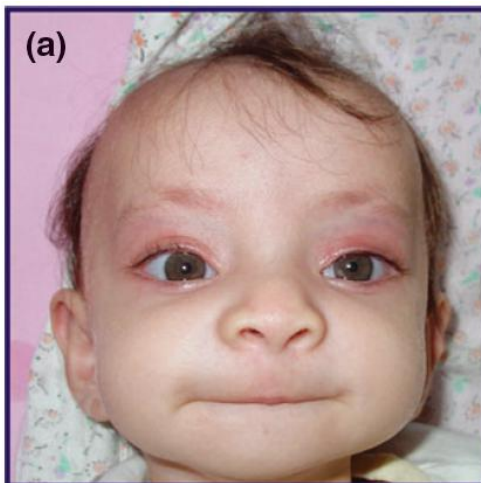
Diagnostic testing:

Genetic testing for mutations in the ADAMTSL2 gene ([612277](#)) on chromosome 9q34.2.

References

1. OMIM WEBSITE:
<http://omim.org/entry/231050.26>
2. Am J Hum Genet July 15 2011;89:7-14.²⁷

Kabuki syndrome (KS1) (OMIM #147920)



Bogershausen N, et al. Clin Genet 2013;83:201–211.²⁸

Clinical characteristics:

Patients often present with a constellation of characteristic facial appearance, short stature, organ malformations and a varying degree of intellectual disability. As infants – failure to thrive is the mainstay and later on growth retardation is significant.

Genetic characteristics:

Mutations in the MLL2 aka KMT2D were found to cause this syndrome. No clear mechanism was established to explain the relation between the genotype and the phenotype.

Common features:

Midface hypoplasia, smooth philtrum and long thin upper lip.

Distinctive features:

Facial: long palpebral fissures, long dense eyelashes and arched eyebrows, prominent ears with hypoplastic helices, depressed nose tip, a full lower lip and the corners of the mouth slant downwards.

Other anomalies:

Includes microcephaly, renal and cardiac malformations, recurrent infections, hearing loss, cleft palate and fingertip pads.

Diagnostic testing:

Genetic testing for any of the known mutations in MLL2 gene.

References

1. Clin Genet 2013;83:201–211.²⁸

Miller Dieker Syndrome (OMIM# 247200)



Clinical characteristics:

Miller–Dieker syndrome (MDS) consists of classical lissencephaly, characteristic facial abnormalities and sometimes other birth defects. Lissencephaly (‘smooth brain’) is a severe malformation of the brain manifest by a smooth cerebral surface, which results from incomplete neuronal migration at 9–13 weeks of fetal development. It is associated with severe mental retardation, epilepsy, spasticity, hypotony, and subtle facial abnormalities. The facial changes consist of prominent forehead, bitemporal hollowing, short nose with upturned nares, flat midface, protuberant upper lip with thin vermilion border and small jaw.

Genetic characteristics:

Usually not inherited. Rearrangements are within chromosome 17p13.3, which can be visible or submicroscopic.

Common features:

Thin vermilion border.

Distinctive features:

Severe mental retardation, epilepsy.

Diagnostic testing:

Genetic testing.

References

1. Hum Mol Genet 1997 Feb;6(2):147-55.²⁹

Noonan Syndrome (NS) (OMIM#163950)



Roberts, et al. Lancet 2013;381:333–42.³⁰

Clinical characteristics:

This multisystem disorder has a genetically based wide clinical variability. Patients usually present with any or all of these features: small stature, congenital heart defects, facial dysmorphism, skeletal malformation and mild intellectual disability.

Genetic characteristics:

Eight genes encoding proteins of the RAS-MAPK signal transduction pathway have been found to cause Noonan syndrome or closely related conditions (*PTPN11*, *SOS1*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, *SHOC2*, and *CBL*). Inheritance is autosomal dominant with variable penetration.

Common features:

Midface hypoplasia, long flat philtrum and narrow upper lip.

Distinctive features:

Facial: broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears.

Other anomalies:

Congenital heart defects (pulmonary valve stenosis, septal defects or cardiomyopathy), pectus excavatum and a webbed neck.

Diagnostic testing:

Genetic testing for mutations in any of the aforementioned genes.

References

1. Lancet 2013;381:333–42.³⁰

Oculodentodigital dysplasia (OMIM #164200)

Clinical features:

Oculodentodigital syndrome is characterized by a typical facial appearance and variable involvement of the eyes, dentition, and fingers. Eye features include microphthalmos, microcornea, and glaucoma. A distinctive physiognomy results from the small nose, small alae nasi and anteverted nostrils, prominent skull, and hypotrichosis. Dental abnormalities include microdontia, enamelogenesis imperfecta, and missing teeth. Digital abnormalities include bilateral camptodactyly or complete syndactyly of the fourth and fifth fingers (syndactyly type III). Neurological symptoms include stiffness and difficulty walking with onset from the first decade to the sixth decade of life, sphincter dysfunction, upper motor neurone involvement with spasticity, hyper-reflexia and positive Babinski sign. Psychomotor retardation is relatively uncommon. Deceleration in head growth, abnormal myelination in the neonatal period, was described.

Genetic features:

Autosomal dominant pattern. The mutation involves gap junction protein alpha 1 (GJA1) encoding the protein connexin 43.

Common features:

Small palpebral fissures.

Distinctive features:

Dental and digital anomalies.

Diagnostic testing:

Molecular genetic testing.

References

1. Eur J Pediatr 2008;167:341–345.³¹

Opitz G/BBB syndrome (OS) (OMIM#145410/300000)



Clinical characteristics:

A constellation of hypertelorism, oral clefts, laryngotracheo-esophageal abnormalities (with resultant hoarse cry, recurrent stridor, swallowing difficulties), genitor-urinary anomalies (such as hypospadias or splayed labia majora), imperforate anus, congenital heart defects and developmental delay.

Genetic characteristics:

May be inherited. X-linked recessive (Xp22) or autosomal (22q11.2) forms, which are clinically indistinguishable. The gene is MID1, which is important to the early development of human midline structures.

Common features:

Smooth philtrum, small palpebral fissures.

Distinctive features:

Other anomalies (laryngotracheo-esophageal abnormalities, genitor-urinary anomalies).

Diagnostic testing:

Genetic testing.

References

1. Nat Genet 1997 Nov;17(3):285-91.³²
2. American Journal of Medical Genetics 2008 Part A;146A:2337–2345.³³

3C (Cranio-Cerebello-Cardiac) aka Ritscher-Schinzel syndrome (OMIM#220210)



Kosaki, et al. American Journal of Medical Genetics 1997;68:421-427³⁴

Clinical characteristics:

Clinical presentation of this rare syndrome generally consists of failure to thrive and craniofacial defects. Further cardiac and neurologic evaluation usually finds a combination of heart defects and cerebellar vermis hypoplasia.

Genetic characteristics:

A pattern of autosomal recessive inheritance was established in this syndrome. The genetic defect is unknown.

Common features:

Midface hypoplasia, low IQ.

Distinctive features:

Facial: prominent occiput, low-set ears, hypertelorism, down-slanting palpebral fissures, depressed nasal bridge and micrognathia.

Other anomalies:

Includes ventricular septal defect, atrial septal defect, tetralogy of Fallot, double outlet right ventricle, hypoplastic left heart, aortic stenosis, pulmonic stenosis and other valvular anomalies, Dandy-Walker malformation, cerebellar vermis hypoplasia and enlargement of the cisterna magna and cleft palate, ocular coloboma.

Diagnostic testing:

There is no diagnostic test for this syndrome.

References:

1. Am J Med Genet 1997;68:421-427.³⁴
2. Am J Med Genet 2001;102:237-242.³⁵

Trisomy 18 (Edward's syndrome) (OMIM #164200)



Clinical features:

Trisomy 18 is the second most common autosomal trisomy observed in live births (1 in 5500 live births).^{23,31} As with trisomy 21, there is a relationship between advanced maternal age and the occurrence of trisomy 18 in offspring due to meiotic nondisjunction. There is a 3:1 female to male ratio among affected infants. The clinical spectrum of trisomy 18 may involve any organ system. The major phenotypic features include growth restriction (IUGR), hypertonia, prominent occiput, small mouth, micrognathia, pointy ears, short sternum, horseshoe kidney, and flexed fingers with the index finger overlapping the third finger and the fifth finger overlapping the fourth. Congenital heart disease occurs in greater than 50 percent of affected individuals with common valvular involvement. Ventricular septal defects and patent duct arteriosus are the most common defects. The gastrointestinal system is involved in about 75 percent of cases. Meckel's diverticulum

and malrotation are the predominant abnormalities. Omphalocele is relatively common prenatally.

Genetic features:

In most cases, nondysjunction of chromosome 18, causing the trisomy.

Common features:

Small palpebral fissures.

Distinctive features:

Typical phenotype of trisomy 18.

Diagnostic testing:

Karyotype.

References

1. Am J Med Genet A 2006 May;140(9):937-44.³⁶
2. Am J Med Genet A 2006 Aug;140(16):1749-56.³⁷

Williams-Beuren syndrome (WBS) (OMIM#194050)



Pober, BR. WBS Review. N Engl J Med 2010;362:239-52³⁸

Clinical characteristics:

Patients may present with facial dysmorphism, growth and mental retardation with varying cardiovascular, endocrine, and nervous systems manifestations.

Genetic characteristics:

In the majority of cases, this syndrome is not inherited, but is the result of a de novo deletion of a large region in chromosome 7, spanning 1.5 million to 1.8 million base pairs. It is estimated that between 26 and 28 genes are affected by this deletion.

Common features:

Midface hypoplasia, long and wide philtrum, thin upper lip, lower than average IQ and ADHD with impulsive trait.

Distinctive features:

Facial: broad forehead, periorbital fullness, stellate pattern of the irises, wide mouth, high rounded cheeks and a pointed chin.

Other anomalies:

Large vessel vascular stenosis, early onset hypertension, hypercalcemia, impaired glucose tolerance especially in adulthood. Language and social skills may be above average, while certain visuospatial skills are poorly developed.

Diagnostic testing:

Molecular and Genetic testing – fluorescence in situ hybridization (FISH) with probes for the gene encoding the elastin protein (ELN) is the most common method. Other available methods are: microsatellite marker analysis, multiplex ligation dependent probe amplification, quantitative polymerase chain reaction (PCR) assay and array comparative genomic hybridization.

References

1. WBS Review. N Engl J Med 2010;362:239-52.³⁸

Fetal Hydantoin Syndrome



http://www.gfmer.ch/genetic_diseases_v2/gendis_detail_list.php?cat3=1627

Clinical characteristics:

Fetal hydantoin embryopathy is characterized by growth retardation, microcephaly, mental retardation and craniofacial dysmorphism

Common features:

Midface hypoplasia, long philtrum and a thin bowed upper lip.

Distinctive features:

Facial: Short nose with anteverted nostrils, broad depressed nasal bridge, redundant inner canthal skin folds and clefting of the lip and/or palate.

Other anomalies:

Include: strabismus, ptosis, ventricular septal defects, hypospadias and inguinal hernias.

Diagnostic testing:

There is no diagnostic test for this syndrome.

References

1. Teratology 1999;59:23–34.³⁹

Fetal Valproate Syndrome



Moore SJ, et al. J Med Genet 2000;37:489-497⁴⁰

Clinical characteristics:

Intra uterine exposure to valproic acid has been shown to induce growth retardation, typical facial manifestations, multiple systemic involvement, and central nervous system dysfunction. This syndrome is distinctly different from those observed after in utero exposure to other anticonvulsant medications.

Common features:

Midface hypoplasia, smooth philtrum and long thin upper lip.

Distinctive features:

Facial: epicanthic folds, infraorbital groove, medial deficiency of the eyebrows, flat nasal bridge, short nose with anteverted nares, a thick lower lip and a small, downturned mouth.

Other anomalies:

Include genital, musculoskeletal and cardiac malformations.

Diagnostic testing:

There is no diagnostic test for this syndrome.

References

1. J Med Genet 2000;37:489-497.⁴⁰
2. Am J Med Genet 2001;98:168-175.⁴¹

Toluene embryopathy



Clinical features:

Toluene (methyl benzene) is an aromatic hydrocarbon, commonly used in the manufacture of paints, organic compounds and others. Exposure to toluene occurs primarily in the occupational setting (where safe levels in air are ≤ 100 PPM). Toluene is also increasingly abused as an inhalant – “solvent sniffing”. Based on several case reports of pregnant women who abused toluene, “toluene embryopathy” was described, and consists of growth retardation, microcephaly, deep set eyes, small palpebral fissures, low set ears, flat nasal bridge, micrognathia and small fingernails. In older children, developmental delay, language impairment, hyperactivity, cerebellar dysfunction and postnatal growth retardation become evident. Importantly, many of the women who abused toluene in pregnancy, also abused alcohol and other drugs such as cocaine. Nevertheless, the syndrome described is most probably related solely to toluene.

Common features:

Facial dysmorphism (flat midface, small palpebral fissures and others), hyperactivity, growth retardation.

Distinctive features:

Maternal history of toluene exposure in the 1st trimester of pregnancy.

Diagnostic testing:

None.

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ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY (ADHD)

Clinical characteristics:

Attention deficit and hyperactivity disorder as defined by the DSM-IV criteria includes inattention on the one hand and hyperactivity and impulsivity on the other hand, both having to be consistent to a degree that is maladaptive and inconsistent with the child’s developmental level. Symptoms must be present for a minimum period of 6 months and they have to be present in different settings and locations, or at least in more than one location, for the diagnosis to be established.

Genetic characteristics:

There are reports of familial tendency but this condition is considered multifactorial and no single gene mutation has been ever associated with it.

Common features:

Low attention span, hyperactivity, impulsive behavior.

Distinctive features:

On physical examination, the lack of dysmorphic features does not rule out FASD as a significant proportion of these children have only neurologic and behavioral problems. Several key publications pointed specific differences that were found between groups of children with FASD and ADHD by the following methods: the California verbal learning test (Crocker et al. 2011), the Controlled Oral Word Association Test and the Trail Making Test (Vaurio et al. 2008) and also the Clinical Observations of Motor and Postural Skills test (Kooistra et al. 2009).

Diagnostic testing:

Commonly used psychological tests are at their best partial diagnostic adjuncts. No gold standard testing method exists for this entity.

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LEARNING DISABILITIES

Clinical characteristics:

This group of learning disabilities is divided into: Reading disorder (ICD-10 and DSM-IV codes: F81.0/315.00), Disorder of Written Expression (ICD-10 and DSM-IV-TR codes 315.2) and Math disability (ICD-10 and DSM-IV codes F81.2-3/315.1). These conditions mostly isolated and have no association with any specific medical problem. School teacher or psychologist will most probably refer the parents for diagnosis.

Genetic characteristics:

There are reports of familial tendency but this condition is considered multifactorial and no single gene mutation has been ever associated with it.

Common features:

One of the psychological hallmarks of FASD is abnormal brain function in at least three of nine brain domains. Of them, several domains including: academic achievements, IQ, memory and executive functioning may be mistakenly perceived as abnormal due to the child's learning disabilities.

Distinctive features:

Facial: On physical examination, the lack of dysmorphic features does not rule out FASD as a significant proportion of these children have only neurologic and psychological problems. These children have no increased rate of impulsive or anti-social behaviour

Diagnostic testing:

Specialized neurocognitive assessment

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OPPOSITIONAL DEFIANT DISORDER (ODD) / CONDUCT DISORDER (CD)

Clinical characteristics:

Issues of aggression, oppositionality and impulsivity, with or without attention deficit or hyperactivity, appear to be the most prevalent psychopathology in children and adolescents, accounting for over 50-70% of referrals to clinics in mental health services. The essential features of CD are a repetitive and persistent pattern of behavior through which the basic rights of others and major age-appropriate societal norms or rules are violated. The essential features of ODD are a recurrent pattern of negativistic, defiant, disobedient and hostile behavior towards authority figures, temper tantrums and irritability. In many

cases, there is a comorbidity between these two conditions. In the DSM-5, CD is defined on the basis of the presence of three of 15 criteria that should have been present in the last 12 months (one must have been present in the past 6 months). These criteria are categorized into four generalized categories: (1) aggression to people and animals, (2) destruction of property, (3) deceitfulness or theft and (4) serious violations of rules. To establish diagnosis, the disturbance in behavior causes clinically significant impairment in social, academic or occupational function. ODD is defined as a pattern of negativistic, hostile, and defiant behavior lasting at least 6 months, during which four (or more) of the following are present: (1) often loses temper, (2) often argues with adults, (3) often actively defies or refuses to comply with adults' requests or rules, (4) often deliberately annoys people, (5) often blames others for his or her mistakes or misbehavior, (6) is often touchy or easily annoyed by others, (7) is often angry and resentful, (8) is often spiteful or vindictive. To establish diagnosis, the disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

Common features:

Aggressiveness, short attention span, disobedience, comorbidity with ADHD.

Distinctive features:

ODD/CD children are older, Child Behavior Checklist (CBCL) questionnaires show that ODD/CD children are more likely to display “cruelty, bullying, meanness to others” and “stealing at home”, while children with FASD are more likely to “act younger”.

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DIFFERENTIAL DIAGNOSIS OF FETAL ALCOHOL SPECTRUM DISORDER

COMPARATIVE TABLE OF MORPHOLOGY

Common feature	Dx Title	What is most similar	Page
Long/ Smooth philtrum	Aarskog syndrome (faciodigitogenital)	Small nose with anteverted nares, broad philtrum, maxillary hypoplasia, and wide-spaced eyes	4
	Cornellia DeLange syndrome	Long philtrum, thin vermilion border, anteverted nares, and depressed nasal bridge	7
	Fetal valproate syndrome	Epicanthal folds, anteverted nares, long philtrum with thin vermilion border, and wide-spaced eyes	22
	Floating harbor syndrome	Smooth filtrum	12
	Geleophysic dysplasia	Smooth filtrum, thin vermilion	13
	Noonan's syndrome	Low nasal bridge, wide-spaced eyes and epicanthal folds	16
	Opitz syndrome	Smooth filtrum, Small palpebral fissures	17
	Toluene embryopathy	Short palpebral fissures, midface hypoplasia, smooth philtrum, and thin vermilion border	24
	Williams syndrome	Short palpebral fissures, anteverted nares, long philtrum, depressed nasal bridge, and epicanthal folds	20
	Short palpebral fissures		
	15q duplication sequence	Small palpebral fissures, short philtrum, autistic behavior	9
	Campomelic dysplasia	Small palpebral fissures	6
	CATCH 22 Syndrome (DiGeorge Synd. + Velocardiofacial Synd)	Facial features (?) and conotruncal heart lesions (?)	8,
	Dubowitz syndrome	Short palpebral fissures, wide spaced eyes, and epicanthal folds	10
	Dubowitz syndrome	Small palpebral fissures, hyperactivity, aggressiveness	10
	Oculodentodigital syndrome	Small palpebral fissures	16
	Opitz syndrome	Smooth filtrum, Small palpebral fissures	17
	Toluene embryopathy	Short palpebral fissures, midface hypoplasia, smooth philtrum, and thin vermilion border	24
	Trisomy 18 syndrome	Small palpebral fissures	19
	Williams syndrome	Short palpebral fissures, anteverted nares, long philtrum, depressed nasal bridge, and epicanthal folds	20
Thin vermilion border	Fetal valproate syndrome	Epicanthal folds, anteverted nares, long philtrum with thin vermilion border, and wide-spaced eyes	22
	FG syndrome	Thin upper lip, hyperactivity	13
	Geleophysic dysplasia	Smooth filtrum, thin vermilion	13
	Maternal PKU fetal effects	Epicanthal folds, short palpebral fissures, long underdeveloped philtrum, and thin vermilion border	23
	Miller Dieker syndrome	thin vermilion	15
	Toluene embryopathy	Short palpebral fissures, midface hypoplasia, smooth philtrum, and thin vermilion border	24
	Other dysmorphic features	Fetal hydantoin syndrome (Fetal dilantin syndrome)	Wide-spaced eyes and depressed nasal bridge
Behavioral features	ADHD	Inattention and hyperactivity	24
	Learning disabilities: -Reading Disorder -Disorder of Written Expression -Math Disability	Poor achievements in any or some of these fields	25
	ODD/CD	Oppositional defiant behavior	25

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