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Fryns Syndrome

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Summary

Disease characteristics. Fryns syndrome is characterized by diaphragmatic defect (hernia, eventration, hypoplasia or agenesis); characteristic facial appearance (coarse facies, ocular hypertelorism, broad and flat nasal bridge, thick nasal tip, long philtrum, low-set and poorly formed ears, tented upper lip, macrostomia, micrognathia); distal digital hypoplasia (nails, terminal phalanges); pulmonary hypoplasia; and associated anomalies (polyhydramnios, cloudy corneas and/or microphthalmia, orofacial clefting, renal dysplasia/renal cortical cysts, and/or malformation involving brain, cardiovascular system, gastrointestinal system, genitalia). Survival beyond the neonatal period is uncommon. Data on postnatal growth and psychomotor development are limited; severe developmental delay and mental retardation are common.

Diagnosis/testing. The diagnosis is based on clinical findings. No genes or loci associated with Fryns syndrome have been identified or mapped.

Management. *Treatment of manifestations:* surgery and/or supportive measures as in the general population. For congenital diaphragmatic hernia, the neonate is immediately intubated to prevent inflation of herniated bowel; additional anomalies may require further consultations and management by a craniofacial team and pediatric specialists in neurology, cardiology, gastroenterology, nephrology. *Surveillance:* depends on the types of malformations present; those with successful congenital diaphragmatic hernia repair should be followed in a specialized center with periodic evaluations by a multidisciplinary team (pediatric surgeon, nurse specialist, cardiologist, pulmonologist, nutritionist).

Genetic counseling. Fryns syndrome is thought to be inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier. Because the gene(s) in which disease-causing mutations occur has/have not been identified, carrier testing and prenatal diagnosis using molecular genetic testing are not available. Two- and three-dimensional ultrasonography and fetal magnetic resonance imaging have been used in the prenatal diagnosis of high-risk pregnancies.

Diagnosis

Clinical Diagnosis

Diagnostic criteria for Fryns syndrome were recently reformulated [Lin et al 2005]. Using these criteria, three categories of individuals with Fryns syndrome are recognized:

- Narrow definition: Presence of four out of six features
- Broad definition: Presence of three of the six features (without facies characteristic of another syndrome)

- Atypical

Note: These categories and the new diagnostic criteria have not yet been prospectively evaluated.

The six proposed criteria are not obligatory (see Note). These are:

- **Diaphragmatic defect** (diaphragmatic hernia in any location, diaphragmatic eventration, significant diaphragm hypoplasia or diaphragm agenesis)
- **Characteristic facial appearance** with a coarse face, ocular hypertelorism, a broad and flat nasal bridge with a thick nasal tip, a long philtrum, low-set and poorly formed ears, a tented upper lip, macrostomia, and micrognathia
- **Distal digital hypoplasia** involving the nails and/or terminal phalanges
- **Pulmonary hypoplasia** of a significant degree
- **Characteristic associated anomalies,** with at least one of the following:
  - Polyhydramnios
  - Cloudy corneas and/or microphthalmia
  - Orofacial clefting
  - Brain malformation
  - Cardiovascular malformation
  - Renal dysplasia/renal cortical cysts
  - Gastrointestinal malformation
  - Genital malformation
- **Affected** sibs (or parental consanguinity) suggesting autosomal recessive inheritance. A detailed three-generation family history should be obtained. Special attention should be paid to similarly affected sibs, other family members with birth defects or physical anomalies, miscarriages, stillbirths or early perinatal deaths, and consanguinity.

Note: Controversies regarding diagnostic criteria include the extent to which phenotypic deviation from the original case reports of Fryns syndrome is tolerable. For example, cases with atypical limb manifestations such as ectrodactyly [Saal & Bulas 1995], radial ray aplasia [Jog et al 2002], limb shortening [Tsukahara et al 1995], and multiple pterygia [Ramsing et al 2000] have been labeled as Fryns syndrome by some authors, but not by others.

Exclusionary criteria. Because chromosomal rearrangements have been associated with CDH and additional major malformations/dysmorphology (see Differential Diagnosis), the diagnosis of Fryns syndrome can only be considered after appropriate chromosome studies have been performed to exclude the following:

- Isochromosome 12p (mosaic tetrasomy 12p; Pallister-Killian syndrome)
- Partial trisomy for chromosome 22q [de Beaufort et al 2000]
- Deletion of chromosome 15q26.2 [Slavotinek et al 2005]
- Deletion of chromosome 8p23.1 [Shimokawa et al 2005, Slavotinek et al 2005]
- Deletion of chromosome 1q41-1q42 [Kantarci, Casavant et al 2006]

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene(s). The causative gene(s) for Fryns syndrome is/are unknown.

Locus (loci). No locus for Fryns syndrome has been mapped, and no linkage data have been reported.

Clinical Description

Natural History

The term Fryns syndrome was first used to describe the clinical findings in two stillborn female siblings, each with a coarse facial appearance, cloudy corneas, a cleft of the soft palate, a small thorax with hypoplastic nipples, proximal insertion of the thumbs, hypoplasia of the terminal phalanges and nails, lung hypoplasia, and congenital diaphragmatic hernia (CDH) with bilateral agenesis of the posterolateral diaphragms. Polyhydramnios was noted in the second trimester of each pregnancy [Fryns et al 1979].

As both of the siblings were stillborn, Fryns syndrome was initially considered likely to be a lethal disorder. It is now known that this is not so. However, the natural history of Fryns syndrome is difficult to determine because of the high mortality. In addition, earlier reports of Fryns syndrome may have mislabeled individuals who either did not have a karyotype or did not have adequate chromosomal studies to evaluate for the chromosome abnormalities associated with a Fryns syndrome-like phenotype (see Diagnosis).

Limited data are available on the survival, postnatal growth, and development of children with Fryns syndrome. No sex difference has been noted.

Survival beyond the neonatal period is uncommon. In children meeting stringent diagnostic criteria, 8/52 (15%) were older than age four weeks at the time of reporting and the oldest was age 15 years [Slavotinek 2004]. Newer treatments for CDH may influence survival. No adults with Fryns syndrome have been reported [Author, personal observation].

Postnatal growth was normal in a child at age 14 months and in another at age seven years; an 18-month old male had macrocephaly with head circumference in the 90th centile, weight in the third centile, and normal stature [Slavotinek 2004]. Growth data were not reported in several other children who survived the neonatal period.

Severe developmental delay and mental retardation formerly were considered invariable in Fryns syndrome [Van Hove et al 1995]. More recently, a few individuals with less severe learning disabilities have been reported, including a one-year old twin who was able to stand with support and to transfer objects, and a two-year old male with hypotonia and mild developmental delay [Slavotinek 2004]. One child began walking at age four years and another walked independently at age six years but remained nonverbal at age nine years. Seizures occurred in at least one child [Cunniff et al 1990].

The prognosis in Fryns syndrome is influenced by the malformations present. Early reports of Fryns syndrome included arhinencephaly, agenesis of corpus callosum, absence of the olfactory bulbs and tracts, hydrocephalus, Dandy-Walker malformation, cleft lip, renal cysts, and hypospadias.

Fryns syndrome has also been reported without CDH [Vasudevan & Stewart 2004, Alessandri et al 2005]. In one review of six individuals with Fryns syndrome (and a normal karyotype) without CDH, all had characteristic facial features, five had distal limb hypoplasia, four had cleft lip and/or palate, and four had cardiac defects [Vasudevan & Stewart 2004]. There were two sib pairs. In another review, the prognosis of individuals with Fryns syndrome was described as more promising in those without CDH [Alessandri et al 2005].

Prevalence

Fryns syndrome was present in seven cases per 100,000 live births in a French population [Aymé et al 1989].

The incidence of Fryns syndrome has been estimated in large cohorts of individuals with congenital diaphragmatic hernia (CDH).

- In one study, 23 of 1,833 persons with CDH observed over a six-year time period were diagnosed with Fryns syndrome (1.3%) [Neville et al 2002].
- Earlier studies estimated the incidence at 4%-10% of persons with CDH.

The variability in incidence can be attributed to different methods of patient ascertainment, the incremental use of cytogenetic studies and molecular genetic testing in diagnosis, and the increasing availability of accurate prenatal diagnosis (e.g., high-resolution sonograms, fetal MRI, prenatal cytogenetic and molecular genetic screening tests) [Neville et al 2002].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Fryns syndrome is the most common autosomal recessive syndrome associated with congenital diaphragmatic hernia (CDH). (See Congenital Diaphragmatic Hernia Overview). Many individuals with CDH and multiple malformations or dysmorphic features have been diagnosed with Fryns syndrome, and there is substantial clinical heterogeneity in the patient group reported to have Fryns syndrome in the published literature. Although a genetic etiology has not yet been established for Fryns syndrome, it is reasonable to assume that genetic heterogeneity is highly likely. The following conditions are distinguishable from Fryns syndrome because of their recognizable patterns of anomalies and the absence of characteristic nail or digital hypoplasia found in Fryns syndrome.

Single-gene disorders in which CDH is observed include the following:

- **Simpson-Golabi-Behmel syndrome (SGBS),** an X-linked disorder associated with mutations in *GPC3*, is characterized by pre- and postnatal macrosomia, distinctive craniofacies (macrocephaly, ocular hypertelorism, macrostomia, macroglossia, palatal abnormalities), and commonly, mild to severe mental retardation with or without structural brain anomalies. Other, variable findings include supernumerary nipples, diastasis recti/umbilical hernia, congenital heart defects, renal defects (nephromegaly, multicystic kidneys, hydronephrosis, hydroureter, duplicated ureters), and GI anomalies (pyloric ring, Meckel's diverticulum, intestinal malrotation, hepatosplenomegaly, hyperplasia of islets of Langerhans, choledochal cysts, polysplenia). In one study, 5/28 (17.8%) of individuals with molecularly confirmed SGBS had CDH [Li et al 2001]. Skeletal anomalies can include vertebral fusion, scoliosis, pectus excavatum, rib anomalies, winged scapula, and congenital hip dislocation. Hand anomalies can include large hands, broad thumbs, brachydactyly, syndactyly, clinodactyly, and postaxial polydactyly. Tumor frequency

is about 10%; reported tumors include Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma.

In addition to X-linked inheritance (and hence typically more severe manifestations in males) and use of molecular genetic testing in diagnosis, SGBS can be distinguished from Fryns syndrome based on the higher frequency of overgrowth, skeletal anomalies, and tumors in SGBS.

- **Cornelia de Lange syndrome (CdLS)** is characterized by distinctive facial features, growth retardation (prenatal onset; <5th centile throughout life), hirsutism, and upper limb reduction defects that range from subtle phalangeal abnormalities to oligodactyly. Craniofacial features include synophrys, arched eyebrows, long eyelashes, small upturned nose, small widely spaced teeth, and microcephaly. IQ ranges from below 30 to 102 with an average of 53. Many individuals demonstrate autistic and self-destructive tendencies. Frequent findings include cardiac septal defects, gastrointestinal dysfunction, hearing loss, myopia, and cryptorchidism or hypoplastic genitalia. CDH was identified in 1/13 (7.7%) of individuals with CdLS [Martinez-Frias et al 1998] from the Spanish Collaborative Study of Congenital Malformations.

  CdLS differs from Fryns syndrome in its distinctive craniofacial features, growth retardation, and upper limb defects. *NIPBL* and *SMC1L1* are the only genes currently known to be associated with CdLS. Molecular genetic testing is clinically available. Inheritance is autosomal dominant *(NIPBL*) and X-linked *(SMC1L1*).

- **Donnai-Barrow syndrome** [OMIM 222448] comprises diaphragmatic defects, omphalocele, agenesis of the corpus callosum, ocular hypertelorism, severe myopia, and sensorineural deafness [Donnai & Barrow 1993]. Cardiac defects, iris coloboma, dysmorphic features with a wide anterior fontanel, downslanting palpebral fissures, epicanthic folds, a short nose with a broad tip and low-set, posteriorly angulated ears, and proteinuria have also been described. Inheritance is autosomal recessive. The causative gene is linked to chromosome 2q23.3-2q31.1 [Kantarci, Donohoe et al 2006].

  Donnai-Barrow syndrome can be clinically distinguished from Fryns syndrome by the ocular hypertelorism, ocular anomalies, enlarged fontanel, and deafness in the former condition.

- **Matthew-Wood syndrome** [OMIM 601186; also known as pulmonary agenesis, microphthalmia, and diaphragmatic defects] is an autosomal recessive condition comprising pulmonary agenesis, microphthalmia, and diaphragmatic defects. Recently, mutations in the *STRA6* gene have been described in individuals with a similar phenotype to Matthew-Wood syndrome comprising anophthalmia and microphthalmia, pulmonary hypoplasia or pulmonary lobe abnormalities, congenital heart defects, diaphragmatic hernia, alveolar capillary dysplasia, renal anomalies, and mental retardation [Pasutto et al 2007]. The *STRA6* gene encodes a transmembrane protein that has been shown to be involved in cellular uptake of retinol [Kawaguchi et al 2007].

  Matthew-Wood syndrome is distinguished from Fryns syndrome by the severe ocular and pulmonary malformations in Matthew-Wood syndrome, combined with absence of the characteristic digital defects found in Fryns syndrome.

Chromosomal conditions associated with CDH and additional major malformations/ dysmorphology have been described and are summarized below. It has been hypothesized that the deleted chromosome regions may harbor a gene for Fryns syndrome, with the condition

resulting from a deletion of the causative gene on one allele and a mutation in the same gene on the other allele.

- **Isochromosome 12p or tetrasomy 12p (Pallister-Killian syndrome, PKS)** [Chiesa et al 1998]. Of all the conditions to be considered in the differential diagnosis, PKS most closely resembles Fryns syndrome. Diaphragmatic hernia can occur in 10%-50% of individuals with PKS [Mowery-Rushton et al 1997]; the facial phenotype is coarse and similar to that of Fryns syndrome.

  Sparse hair is characteristic of PKS, in contrast to Fryns syndrome in which the sisters originally described by Fryns had low hairlines and hypertrichosis [Fryns et al 1979]. Other features observed in PKS but not in Fryns syndrome are syndactyly and streaky skin pigmentation, whereas distal digital hypoplasia, cloudy corneas, and internal malformations are seen in Fryns syndrome and not PKS [McPherson et al 1993].

  In some persons, only chromosome analysis and/or the inheritance pattern can distinguish between PKS and Fryns syndrome [Paladini et al 2000, Veldman et al 2002]. To evaluate for PKS, skin fibroblasts, chorion villus cells, or amniocytes should be karyotyped because of the phenomenon of tissue-specific mosaicism in which the isochromosome 12p can be present in some cells (e.g., fibroblasts), but not others (e.g., lymphocytes). It is important to note that a normal karyotype on peripheral blood lymphocytes does not exclude PKS.

- **Monosomy 15q26.** More than 25 persons with CDH and an interstitial or terminal deletion of distal chromosome 15q have been reported [Biggio et al 2004; Castiglia et al 2005; Klaassens, Tibboel et al 2005; Klaassens, van Dooren et al 2005; López et al 2006; Slavotinek et al 2006]. Deletions of chromosome 15q have been estimated to account for up to 1% of persons with CDH [Klaassens, van Dooren et al 2005]. The phenotype associated with 15q26 deletions is recognizable and has been considered to constitute a contiguous gene deletion syndrome. The cardinal clinical findings are diaphragmatic defects (19/21 or 90%; most commonly herniation, but hypoplasia of the diaphragm has also been described), pulmonary hypoplasia (8/16 or 50%), severe growth retardation (16/17 or 94%), cardiovascular malformations comprising ventricular septal defect (8/19 or 42%), aortic stenosis (4/19 or 21%) and hypoplasia of the left heart (2/19 or 11%), facial dysmorphism (8/16 or 50%), talipes and/or rockerbottom feet (6/16 or 38%) and a single umbilical artery (5/16 or 31%) [Slavotinek et al 2006]. Nail hypoplasia was present in only 2/16 (13%). The severe growth retardation, type of cardiac defects, talipes, and/or rockerbottom feet, and single umbilical artery are all distinctive features in this deletion syndrome. This phenotype, with or without a diaphragmatic hernia, should be a clear indication for FISH studies for 15q26.2 deletions, even if a G-banded karyotype has been normal. Cases without diaphragmatic hernia but with a similar deletion are less common [Klaassens, van Dooren et al 2005].

- **Monosomy 8p23.1.** Interstitial deletions of chromosome 8p23.1 have also been associated with CDH and additional anomalies [Faivre et al 1998, Borys & Taxy 2004, Shimokawa et al 2005, Slavotinek et al 2005, López et al 2006]. However, one study described diaphragmatic hernias in only 4/18 individuals with monosomy for chromosome 8p23.1 [Faivre et al 1998]; thus an 8p23.1 deletion is a predisposing pathogenic factor for CDH but may not necessarily cause it.

  The phenotype associated with interstitial deletions of 8p23.1 commonly includes congenital heart defects (atrioventricular septal defects and atrial and ventricular septal defects), genitourinary anomalies with cryptorchidism, developmental delays and mild to moderate mental retardation, growth retardation, facial dysmorphism, and

strabismus [Faivre et al 1998, Shimokawa et al 2005, Slavotinek et al 2005, López et al 2006]. The heart malformations are the most characteristic finding.

- **Monosomy 1q41-1q42.** A third locus for a Fryns syndrome-like phenotype was also identified during a study of 29 individuals with CDH and normal karyotypes by array-comparative genomic hybridization [Kantarci, Casavant et al 2006]. The paper described a 5-Mb *de novo* deletion between clones RP11-553F10 and RP11-275O4 at chromosome 1q41-1q42.13 in a child with a large, left congenital diaphragmatic hernia (CDH) and mild right-sided diaphragmatic eventration, pulmonary hypoplasia, facial dysmorphism with large fontanelles, hypertelorism, a broad nasal tip, a tented upper lip and a cleft of the soft palate, a small muscular ventricular septal defect, hypoplasia of the nails, talipes equinovarus, and possible partial suproglottic and glottic luminal stenosis [Kantarci, Casavant et al 2006]. A male with a larger, paternally derived overlapping interstitial deletion at chromosome 1q32.3-1q42.2 detected on a G-banded karyotype also had CDH [Slavotinek et al 2006]. This individual had pulmonary hypoplasia, a double-outlet right ventricle and a ventricular septal defect, bilateral cleft lip and palate, a cystic hygroma, facial dysmorphism, bilateral hydronephrosis, cryptorchidism, and talipes equinovarus in addition to the hernia.

  Two additional individuals reported to have *de novo* interstitial deletions of chromosome 1q42 and diaphragmatic hernia on chromosome analysis have not been molecularly studied. A female with diaphragmatic hernia and multiple malformations had a karytoype of 46,XX,del(1)(pter↓q42.11::q42.3↓qter), with normal FISH studies for the 1q telomeres [Rogers et al 1995] and a newborn male with diaphragmatic hernia and pulmonary hypoplasia had a maternally derived 1q deletion with karytyope 46,XY,del(1) (pter↓q32.31::q42.3↓qter) [Youssoufian et al 1988]. However, as for monosomy 8p23.1, diaphragmatic hernias are present in a minority of those with 1q42 deletions.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease following diagnosis, the neonate should be screened for additional physical anomalies as completely as possible:

- Chest and abdominal radiographs
- Cranial ultrasound examination
- Echocardiogram
- Renal ultrasound examination
- Examination for dysmorphic features and digital anomalies by a clinical geneticist

Depending on the clinical situation, further cranial evaluation with an MRI scan, a complete radiographic skeletal survey and a detailed ophthalmology examination should be considered to evaluate for other physical findings that could be present.

Evaluation by a clinical geneticist and developmental pediatrician is recommended.

Treatment of Manifestations

The physical manifestations of Fryns syndrome can be treated by surgery and/or supportive measures in the same way that the same manifestations are treated when they are not part of a syndrome. However, treatment of the diaphragmatic hernia often takes precedence over the management of other anomalies present.

For congenital diaphragmatic hernia (CDH), the neonate is immediately intubated to prevent inflation of herniated bowel.

Medical therapies are used to stabilize the infant prior to surgical repair. High-frequency oscillatory ventilation and extra-corporeal membrane oxygenation (ECMO) have achieved recent popularity. Nitric oxide, surfactant and perflubron have also been tried, but the efficacy of these measures has not been systematically evaluated.

In Fryns syndrome, additional anomalies may dictate further consultations; management by a pediatric neurologist, pediatric cardiologist, pediatric gastroenterologist, pediatric nephrologist, and a craniofacial team may be appropriate.

See also Congenital Diaphragmatic Hernia Overview.

Surveillance

In those who survive the neonatal period, surveillance depends on the types of malformations present and is specific to each individual.

Infants with successful CDH repair should be followed by a multidisciplinary team at a specialized center, with periodic evaluations by a pediatric surgeon, nurse specialist, cardiologist, pulmonologist, and nutritionist.

Testing of Relatives at Risk

Testing of sibs at risk for Fryns syndrome requires an evaluation for physical anomalies (see Diagnosis and Management: Evaluations Following Initial Diagnosis). If chromosome studies were **not** obtained on the proband, a high-resolution karyotype to evaluate for the possibility of a chromosome disorder (see Differential Diagnosis) could be performed in the sib(s) at risk. A high index of suspicion for a chromosomal aberration should prompt exclusion of deletions at the chromosomal loci associated with a Fryns syndrome-like phenotype.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

There are no specific therapies under investigation for Fryns syndrome. However, there are many different treatments that are being evaluated for the management of congenital diaphragmatic hernia.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

For a more detailed discussion on the management of congenital diaphragmatic hernia, see Congenital Diaphragmatic Hernia Overview.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Fryns syndrome is thought to be inherited in an autosomal recessive manner. See Table 1.

Table 1. Fryns Syndrome: Selected Evidence in Support of Autosomal Recessive Inheritance

	Number of Sibs	Consanguineous Relationship	Type of Chromosome Study Performed [1]	Citation
Consanguineous cases	One male	Second cousins	1	Fitch et al 1978
	One female	First cousins once removed	1, 2	Meinecke & Fryns 1985
	One male	First cousins	1	Dix et al 1991
	One brother, one sister	Second cousins	1	Kershisnik et al 1991
	One brother, one sister	First cousins	2 on affected female; 1 on affected male	Wilgenbus et al 1994
	Two affected sibs: one male and one with sex unknown	Second cousins	1 with FISH for 22q11 deletions on affected male	Vasudevan & Stewart 2004
Non-consanguineous cases with more than one affected sibling	Three brothers, one sister	N/A	1 in both parents and two affected sibs	Samueloff et al 1987
	One brother, one sister		1 in both affected sibs	Moerman et al 1988
	One brother, one sister		1 in two affected sibs	Aymé et al 1989
	Two brothers		1, 2 in one affected male	Cunniff et al 1990
	Two brothers		2 in one affected male; 3 in both	Ramsing et al 1991 (family 1)
	Three affected sibs: two sisters, one brother		2; exclusion of tetrasomy 12p and trisomy 22 by microsatellite markers	Ramsing et al 1991 (family 2)
	Three affected sibs: two brothers and one of unknown sex		1 in both males	Langer et al 1994
	Monozygous male twins		1 on one male; 2 on both	Vargas et al 2000

Using broad diagnostic criteria (i.e., including those without diaphragmatic hernia; see Lin et al 2005)

1. Type of chromosome study performed:

    1. Chromosome analysis, band resolution not stated
    2. Karyotype of skin biopsy or, if anomalies are detected prenatally, of amniocytes or chorionic villus cells
    3. Comparative genomic hybridization (not array) Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore each carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. No reports of reproduction in individuals with Fryns syndrome have been published.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Because the gene(s) in which disease-causing mutations occur has/have not been identified, carrier testing is not available.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the gene(s) in which disease-causing mutations occur has/have not been identified. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Because the gene(s) in which disease-causing mutations occur has/have not been identified, prenatal molecular genetic testing is not available.

A priori high-risk pregnancy (i.e., sib with Fryns syndrome)

Ultrasound examination. Fryns syndrome has been diagnosed by two- and three-dimensional ultrasonography and fetal magnetic resonance imaging (MRI) [Benacerraf et al 2006]. Characteristic features in one infant included a right diaphragmatic hernia, cleft soft palate, renal dysgenesis, and a bicornuate uterus with a normal karyotype [Benacerraf et al 2006]. The newer, three-dimensional scans may also allow a more detailed assessment of facial features. Findings on ultrasound examination in addition to a diaphragmatic hernia and pulmonary hypoplasia that may suggest a diagnosis of Fryns syndrome include polyhydramnios in the second trimester, cardiac malformations such as ventricular and atrial septal defects, renal cysts, hydroureter, ventricular dilatation/hydrocephalus, agenesis of the corpus callosum, and Dandy-Walker malformation.

Thus, a detailed sonographic examination of the fetus with echocardiography and measurement of growth parameters and amniotic fluid levels is recommended. Fetal MRI should be considered to confirm the presence of a diaphragmatic defect and to search for other anomalies.

A priori high-risk pregnancy (i.e., sib with possible Fryns syndrome)

Chromosome analysis. If chromosome analysis was not performed on the sib with Fryns syndrome (i.e., the diagnosis may be a chromosomal syndrome associated with CDH and additional major malformations/dysmorphology), chromosome analysis of fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation should be considered.

Wherever possible, the chromosome analysis performed for an evaluation of possible Fryns syndrome should include FISH for deletion 22q11.2, FISH using subtelomeric probes for subtelomeric chromosome aberrations, and array-comparative genomic hybridization, preferably using an array that contains probes for the 15q26 and 1q41-1q42 regions that are deleted in some individuals with CDH and additional malformations/dysmorphology (see Differential Diagnosis).

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

A priori low-risk pregnancy (i.e., no family history of Fryns syndrome). A routine prenatal ultrasound examination may identify a diaphragmatic hernia and other malformations raising the possibility of Fryns syndrome in a fetus not known to be at risk. In such situations, chromosome analysis to evaluate the fetus for a chromosome abnormality (see Chromosome analysis) is recommended. Confirmation of the diagnosis of Fryns syndrome, however, may not be possible prior to delivery, pending evaluation with complete physical examination and other imaging studies.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. OMIM Entries for Fryns Syndrome

229850	FRYNS SYNDROME; FRNS

Molecular Genetic Pathogenesis

Chromosome deletions involving chromosomes 15q26.2, 8p23.1, or 1q41-1q42 [Kantarci, Casavant et al 2006] in individuals with CDH and additional major malformations/ dysmorphology have led to the hypothesis that in some instances Fryns syndrome may result from a contiguous gene deletion syndrome involving genes at these loci.

However, autosomal recessive inheritance is most likely the cause of Fryns syndrome (see Table 1). The observations summarized in Table 1 argue for the involvement of at least one autosomal recessive gene in the etiology of Fryns syndrome. In addition, the diversity of the limb malformations in Fryns syndrome suggests that mutations in more than one gene could be causative. However, no published data to support either hypothesis are available.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

CHERUBS-The Association of Congenital Diaphragmatic Hernia Research, Advocacy, and Support
270 Coley Road
Henderson NC 27537
Phone: 252-492-6003
Fax: 815-425-9155
Email: info@cherubs-cdh.org
www.cherubs-cdh.org

Compassionate Friends
PO Box 3696
Oak Brook IL 60522-3696
Phone: 877-969-0010; 630-990-0010
Fax: 630-990-0246
Email: nationaloffice@compassionatefriends.org
www.compassionatefriends.org

Helping After Neonatal Death (HAND)
A non-profit California-based group that lists support groups
www.handonline.org/resources/groups/index.html

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

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Suggested Readings

Alkuraya FS, Lin AE, Irons MB, Kimonis VE. Fryns syndrome with Hirschsprung disease: support for possible neural crest involvement. Am J Med Genet A. 2005;132:226–30. [PubMed: 15580636]

Chapter Notes

Revision History

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