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Fryns Syndrome

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Summary

Clinical characteristics

Fryns syndrome is characterized by diaphragmatic defects (diaphragmatic hernia, eventration, hypoplasia, or agenesis); characteristic facial appearance (coarse facies, wide-set eyes, a wide and depressed nasal bridge with a broad nasal tip, long philtrum, low-set and anomalous ears, tented vermilion of the upper lip, wide mouth, and a small jaw); short distal phalanges of the fingers and toes (the nails may also be small); pulmonary hypoplasia; and associated anomalies (polyhydramnios, cloudy corneas and/or microphthalmia, orofacial clefting, renal dysplasia / renal cortical cysts, and/or malformations involving the brain, cardiovascular system, gastrointestinal system, and/or genitalia). Survival beyond the neonatal period is rare. Data on postnatal growth and psychomotor development are limited; however, severe developmental delay and intellectual disability are common.

Diagnosis/testing

The clinical diagnosis of Fryns syndrome can be established in a proband based on six proposed criteria (diaphragmatic defect, characteristic facial appearance, distal digital hypoplasia, pulmonary hypoplasia, at least one characteristic associated anomaly, and a family history consistent with autosomal recessive inheritance). The molecular diagnosis can be established in a proband with suggestive findings and biallelic pathogenic variants in *PIGN* identified by molecular genetic testing.

Management

Treatment of manifestations: For congenital diaphragmatic hernia, the neonate is immediately intubated to prevent inflation of herniated bowel, surgery, and/or supportive measures as for the general population. Standardized treatment with anti-seizure medications by an experienced neurologist. Additional anomalies may require consultations and management by ophthalmology, cardiology gastroenterology, nephrology, urology, and craniofacial specialists. Developmental services as needed including feeding, motor, adaptive, cognitive, and speech/language therapy.

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Surveillance: 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). Monitor those with seizures as clinically indicated.

Assess for new onset of seizures. Monitor developmental progress and educational needs. Follow up with ophthalmology, cardiology, gastroenterology, nephrology, urology, and craniofacial specialists as needed.

Genetic counseling

Fryns syndrome is 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% of being unaffected and not a carrier. Heterozygotes (carriers) are asymptomatic. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the *PIGN* pathogenic variants in the family are known.

Diagnosis

Diagnostic criteria for Fryns syndrome were reformulated by Lin et al [2005] to include the six proposed clinical criteria described in Suggestive Findings: diaphragmatic defect, characteristic facial appearance, distal digital hypoplasia, pulmonary hypoplasia, at least one characteristic associated anomaly, and family history consistent with autosomal recessive inheritance.

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, radial ray aplasia, limb shortening, and multiple pterygia have been labeled as Fryns syndrome by some authors, but not by others.

Suggestive Findings

Diagnosis of Fryns syndrome **should be suspected** in individuals with the following clinical and laboratory findings.

Clinical findings

- **Diaphragmatic defects** including diaphragmatic hernia in any location (most commonly a posterolateral Bochdalek hernia), diaphragmatic eventration, significant diaphragm hypoplasia, or diaphragm agenesis
- **Characteristic facial appearance** with a coarse face, wide-set eyes, a wide and depressed nasal bridge with a broad nasal tip, a long philtrum, low-set and anomalous ears, a tented vermilion of the upper lip, wide mouth, and a small jaw
- **Short distal phalanges** of the fingers and toes. The nails may also be small.
- **Pulmonary hypoplasia** of a significant degree. This clinical finding can accompany diaphragmatic hernia.
- **Characteristic associated anomalies** including at least one of the following:
  - Polyhydramnios
  - Cloudy corneas and/or microphthalmia
  - Orofacial clefting
  - Brain malformations including hydrocephalus, abnormalities of the corpus callosum, and Dandy-Walker malformation
  - Cardiovascular malformation
  - Renal dysplasia / renal cortical cysts
  - Gastrointestinal malformation
  - Genital malformation

- **Family history consistent with autosomal recessive inheritance** (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Laboratory findings. Absence of a copy number variant associated with congenital diaphragmatic hernia, including chromosome deletions at 15q26.2 and 8p23.1 and mosaic trisomy 1q [Bone et al 2017]. See Differential Diagnosis and Yu et al [2012] and Yu et al [2020] for review.

Establishing the Diagnosis

The clinical diagnosis of Fryns syndrome can be **established** in a proband based on clinical diagnostic criteria [Slavotinek 2004, Lin et al 2005], or the molecular diagnosis can be established in proband with suggestive findings and biallelic pathogenic variants in *PIGN* identified by molecular genetic testing (see Table 1).

Clinical diagnosis. Diagnostic criteria for Fryns syndrome were reformulated by Lin et al [2005] to include the six proposed criteria described in Suggestive Findings: diaphragmatic defect, characteristic facial appearance, distal digital hypoplasia, pulmonary hypoplasia, at least one characteristic associated anomaly and family history consistent with autosomal recessive inheritance.

Molecular diagnosis. The molecular diagnosis of Fryns syndrome **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PIGN* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *PIGN* variants of uncertain significance (or of one known *PIGN* pathogenic variant and one *PIGN* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas comprehensive genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings can be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with multiple congenital anomalies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *PIGN* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *PIGN* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or

custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by multiple congenital anomalies, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is most likely to be used. **Exome sequencing** is most common; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Fryns Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PIGN	Sequence analysis [3]	10 individuals [4]
	Gene-targeted deletion/duplication analysis [5]	1 reported [6]
Unknown	NA	See footnote 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Brady et al [2014], McInerney-Leo et al [2016], Alessandri et al [2018]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. 5.07-kb deletion with breakpoints in exon 5 and intron 7 (See Table 8.)
7. Genetic heterogeneity for Fryns syndrome remains highly probable, as some individuals with a clinical diagnosis of Fryns syndrome have not had *PIGN* pathogenic variants identified [McInerney-Leo et al 2016]. The number of individuals meeting the clinical diagnostic criteria for Fryns syndrome with negative testing for *PIGN* variants is unknown.

Clinical Characteristics

Clinical Description

The term "Fryns syndrome" was first used to describe the clinical findings in two stillborn female sibs, 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 [Fryns et al 1979]. As both of the sibs 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 early mortality. In addition, earlier reports of Fryns syndrome may have mislabeled individuals who either did not have chromosome analysis or did not have adequate laboratory studies to evaluate for copy number variants associated with a Fryns syndrome-like phenotype (see Differential Diagnosis).

Recently, biallelic variants in *PIGN* have been identified in individuals who met the strict diagnostic criteria for Fryns syndrome [Brady et al 2014, McInerney-Leo et al 2016, Alessandri et al 2018] as described in Establishing

the Diagnosis [Lin et al 2005]. As only ten individuals have been identified with biallelic pathogenic variants in *PIGN* and a Fryns syndrome phenotype [Alessandri et al 2018], the extent of the contribution of this gene to the etiology of Fryns syndrome is not yet known; in addition, it is also unclear if the clinical description of this syndrome should be modified based on the phenotype associated with *PIGN* variants.

The following description of the phenotypic features associated with this condition is based on reports of individuals with a clinical diagnosis of Fryns syndrome and those with a molecular diagnosis of Fryns syndrome caused by biallelic pathogenic variants in *PIGN* [Brady et al 2014, McInerney-Leo et al 2016, Alessandri et al 2018].

Table 2. Fryns Syndrome: Frequency of Select Features

Feature	Proportion of Persons w/Feature		Comment
	Persons w/a clinical diagnosis of Fryns syndrome [1]	Persons w/biallelic *PIGN* pathogenic variants [2]	
Polyhydramnios	56%	6/10	
Diaphragmatic hernia	>90%	7/10	
Structural brain malformations	88%	3/10	
Ocular anomalies	>6% [3]	2/6	
Cardiac anomalies	>40% [3]	6/10	
Gastrointestinal anomalies	>15% [3]	Not established	
Genitourinary anomalies	>25% [3]	5/10	
Dysmorphic features	>55% [3]	8/10	
Distal digital hypoplasia	>60% [3]	8/10	
Developmental delay	Unknown due to poor survival	NA	Perinatal death in 10/10 persons w/*PIGN* pathogenic variants

1. *PIGN* testing status is not known for these individuals.
2. Alessandri et al [2018]
3. Slavotinek [2004]

Prenatal findings. CDH and the other malformations found in Fryns syndrome can be visualized by ultrasound scan in the prenatal period, usually from the second trimester, but the diagnosis of Fryns syndrome is rarely established prior to birth [Peron et al 2014] and requires appropriate cytogenetic and molecular genetic testing. Prenatal findings in those with *PIGN* variants have included nuchal translucency, severe septated cystic hygromata, fetal ascites, a small exomphalos, moderately hyperechogenic bowel, echogenic kidneys, and femur length at the fifth centile [McInerney-Leo et al 2016]. Polyhydramnios has also been noted in the second and third trimester and has been described as "massive" [Alessandri et al 2018].

Survival/prognosis. The prognosis in Fryns syndrome is influenced by the malformations present and has been described as more promising in those without CDH than in those with CDH. Survival beyond the neonatal period is uncommon both in those with a clinical diagnosis of Fryns syndrome and in individuals with biallelic *PIGN* variants (none of whom survived the neonatal period). No sex differences have been noted.

Diaphragmatic abnormality / respiratory concerns. CDH is found in more than 90% of individuals with a clinical diagnosis of Fryns syndrome [Peron et al 2014]. A unilateral, left-sided Bochdalek hernia is most commonly observed. Diaphragmatic defects were identified in 50% of individuals with *PIGN* pathogenic variants. Abnormal pulmonary lobation was also noted in one individual.

Neurologic findings. Structural brain malformations in those with *PIGN* pathogenic variants have included thinning and shortening of the corpus callosum, hypoplasia of the cerebellar vermis, and agenesis of the olfactory bulbs.

Ocular findings. Eye findings previously associated with Fryns syndrome have included central/paracentral corneal clouding that may result from abnormal corneal endothelium, microphthalmia, irregularities of Bowman's layer, thickened posterior lens capsule, and retinal dysplasia [Cursiefen et al 2000]. In those with *PIGN* pathogenic variants, cloudy corneas and cataracts have been described.

Cardiac findings. In individuals diagnosed clinically with Fryns syndrome, ventricular septal defect was the most frequently observed cardiac malformation; atrial septal defects and aortic abnormalities have also been reported. In individuals with *PIGN* pathogenic variants, tetralogy of Fallot, ventricular septal defect, patent ductus arteriosus, overriding aorta, hypoplastic pulmonary trunk, and an aberrant retro-esophageal right subclavian artery have been described. One fetus had a mildly hypoplastic right ventricle with pulmonary valve stenosis and narrowed pulmonary trunk, membranous ventricular septal defect, and an aberrant right subclavian artery arising distal to the left subclavian artery.

Gastrointestinal findings. Abdominal defects have included exomphalos and intestinal malrotation in individuals with *PIGN* pathogenic variants. Anal malformations have been noted in individuals with a clinical diagnosis of Fryns syndrome, but not reported in those with *PIGN* pathogenic variants.

Genitourinary findings. Renal pyelectasis, segmental renal dysplasia, micropenis, and cryptorchidism have been reported in individuals with *PIGN* pathogenic variants. Hypospadias and bicornuate uterus as seen in individuals diagnosed clinically with Fryns syndrome have not been reported to date in association with *PIGN* pathogenic variants.

Dysmorphic findings. The most characteristic facial features for individuals with a clinical diagnosis of Fryns syndrome include a coarse face, wide-spaced eyes with cloudy corneas, a wide and flat nasal bridge with anteverted nares, anomalous and low-set ears, macrostomia, and a small jaw. Facial features in individuals with *PIGN* pathogenic variants have been described as coarse with wide-spaced eyes, a small nose, flat nasal bridge, anteverted nares, a long philtrum, macrostomia, and small low-set anomalous ears. Clefts of the lip and palate have also been noted. One fetus had mild axillary pterygia and a synovial cyst attached to the left heel [Brady et al 2014].

Skeletal findings. Small nails and short terminal phalanges of the fingers and toes are frequent and useful diagnostic findings in Fryns syndrome. In individuals with *PIGN* pathogenic variants, short thumbs and fingers (most pronounced for the fifth finger), short toes, and small or absent nails were reported. Unilateral talipes was also described. One male with *PIGN* pathogenic variants had oligodactyly of the left foot, with absence of rays three to five, hypoplasia of the remaining toes, and absent toenails [Brady et al 2014], which would be considered atypical for Fryns syndrome. Nail defects were not present in all individuals [McInerney-Leo et al 2016].

Development. Developmental delay ranging from relatively mild impairment to severe intellectual disability has been reported in individuals with clinically diagnosed Fryns syndrome. Due to impaired survival, the developmental course is not known for those with Fryns syndrome caused by *PIGN* pathogenic variants.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *PIGN*-related Fryns syndrome have been identified.

Prevalence

Fryns syndrome was present in seven of 100,000 live births in a French population [Aymé et al 1989], but this prevalence was established before the advent of many genetic testing methodologies. No more recent prevalence estimates have been published.

Fryns syndrome may be the most common autosomal recessive disorder associated with congenital diaphragmatic hernia (CDH); see Congenital Diaphragmatic Hernia Overview). The incidence of Fryns syndrome has been estimated in large cohorts of individuals with CDH.

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

Some individuals with *PIGN*-related Fryns syndrome have shared ancestry from La Réunion and other Indian Ocean islands, with a founder effect considered likely for a pathogenic, intragenic deletion [Alessandri et al 2018] (see Molecular Genetics).

Genetically Related (Allelic) Disorders

Biallelic pathogenic variants in *PIGN* are also known to cause **multiple congenital anomalies-hypotonia-seizures syndrome** (MCAHS1) (OMIM 614080). Both MCAHS1 and Fryns syndrome are associated with polyhydramnios, coarse facies with a high-arched palate, flat nasal bridge and anomalous ears, short phalanges and small nails, and genitourinary, gastrointestinal, and cardiac defects. MCAHS1 can be differentiated from Fryns syndrome by the absence of diaphragmatic hernia and a less severe presentation [Alessandri et al 2018].

Almost all known MCAHS1-related *PIGN* pathogenic variants are missense or compound missense/loss-of-function variants, whereas *PIGN* pathogenic variants associated with Fryns syndrome are predicted to result in loss of function [McInerney-Leo et al 2016, Alessandri et al 2018].

Differential Diagnosis

Disorders associated with complex congenital diaphragmatic hernia (CDH) may resemble Fryns syndrome, but are distinguishable from Fryns syndrome by their recognizable patterns of anomalies and an absence of characteristic nail or digital hypoplasia. See Table 3.

Table 3. Monogenic Disorders Associated with Complex Congenital Diaphragmatic Hernia of Interest in the Differential Diagnosis of Fryns Syndrome

Gene(s)	Differential Disorder	MOI	CDH [1]	Other Characteristic Features
GPC3 *GPC4* [2]	Simpson-Golabi-Behmel syndrome type 1 (SGBS1)	XL	Rare	• Overgrowth (pre- & postnatal), macrocephaly, dysmorphic features (coarse facies, macrostomia, wide-set eyes, palatal abnormalities), polydactyly, syndactyly, CHD & mild-to-severe ID ± structural brain anomalies • Overgrowth, skeletal anomalies, & tumors distinguish SGBS1 from Fryns syndrome. [3]
EFNB1	Craniofrontonasal syndrome (CFNS) (OMIM 304110)	XL	Rare (can occur in both males & females w/ CFNS)	Coronal synostosis, facial anomalies (wide-set eyes, wide nasal tip), & skeletal anomalies

Table 3. continued from previous page.

Gene(s)	Differential Disorder	MOI	CDH [1]	Other Characteristic Features
PORCN	Focal dermal hypoplasia (Goltz syndrome)	XL	Rare	Linear skin pigmentation, fat herniation, eye anomalies incl microphthalmia, small teeth, digital anomalies
BRD4 *HDAC8* *NIPBL* [4] *RAD21* *SMC1A* *SMC3*	Cornelia de Lange syndrome (CdLS)	AD XL	Rare	Facial anomalies (high-arched &/or joined eyebrows, long eyelashes, short nose w/anteverted nares, small & widely spaced teeth), microcephaly, growth restriction, hirsutism, upper-limb reduction defects, ID, autistic features, self-destructive behavior
WT1	*WT1* disorder (incl Denys-Drash syndrome, Frasier syndrome, Meacham syndrome) [5]	AD	Rare	Urogenital anomalies, Wilms tumor, nephropathy, glomerulopathy, disorders of sexual development
FBN1	Marfan syndrome	AD	Rare	Musculoskeletal, cardiac, & ocular defects; diaphragmatic eventration & hernia can be assoc w/ early-onset Marfan syndrome. [6]
NR2F2	Congenital heart defects, multiple types, 4 (OMIM 615779)	AD	Variable	Fryns syndrome-like craniofacial anomalies, cardiovascular malformations, hypoplastic genitalia or cryptorchidism, severe prenatal growth deficiency, ID, talipes equinovarus &/or rockerbottom feet, single umbilical artery
LRP2	Donnai-Barrow syndrome	AR	Core feature	Facial anomalies (wide-set eyes, enlarged anterior fontanelle); high myopia, retinal detachment, progressive vision loss, iris coloboma, sensorineural deafness; agenesis of corpus callosum; omphalocele; ID
RARB *STRA6*	Matthew-Wood syndrome (PDAC syndrome; syndromic microphthalmia) (OMIM 615524, 601186)	AR AD	Core	• Micro-/anophthalmia, pulmonary agenesis or hypoplasia, CHD, genitourinary anomalies • Matthew-Wood syndrome is not assoc w/ small nails or small digits.

AD = autosomal dominant; AR = autosomal recessive; CDH = congenital diaphragmatic hernia; CHD = congenital heart defect; ID = intellectual disability; MOI = mode of inheritance; PDAC = *p*ulmonary hypoplasia/agenesis, *d*iaphragmatic hernia/eventration, *a*nophthalmia/microphthalmia, & *c*ardiac defect; XL = X-linked

1. See also Congenital Diaphragmatic Hernia Overview.

2. SGBS1 is caused by a pathogenic variant in *GPC3*, an intragenic or whole-gene deletion of *GPC3* that may include part or all of *GPC4*, or a large multiexon duplication of *GPC4*.

3. Individuals with SGBS are at increased risk for embryonal tumors including Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma.

4. CDH occurring in CdLS is typically associated with pathogenic variants in *NIPBL* [Yu et al 2020].

5. Frasier syndrome, Denys-Drash syndrome, and Meacham syndrome were originally described as distinct disorders on the basis of clinical findings but are now understood to represent a continuum of features caused by a *WT1* heterozygous pathogenic variant.

6. Veiga-Fernández et al [2020]

Table 4. Chromosome Anomalies Associated With Congenital Diaphragmatic Hernia and Additional Major Malformations/ Dysmorphology

Chromosome Abnormality	Critical Genes Included	Facial Phenotype	Other Clinical Characteristics (in addition to CDH)
Pallister-Killian syndrome (PKS) [1] (mosaic tetrasomy 12p) (OMIM 601803)		• Coarse w/wide-set eyes, prominent cheeks, & eversion of vermilion of lower lip • Considered similar to Fryns syndrome [2, 3]	• Sparse hair, [4] syndactyly, & streaky skin pigmentation • Hypotonia, seizures, & ID common [3] • Short distal phalanges of fingers & toes, small nails, cloudy corneas, CHD, & internal malformations may be seen but are typically less frequent in PKS than in Fryns syndrome.
Del 15q26.2 (OMIM 142340)	*NR2F2* [5]	Fryns syndrome-like craniofacial anomalies	CHD, hypoplastic genitalia or cryptorchidism, severe prenatal growth deficiency, ID, talipes equinovarus &/or rockerbottom feet, single umbilical artery
Del 8p23.1 (OMIM 222400)	*GATA4* *SOX7* [5]	Mild facial anomalies	CHD (e.g., heterotaxy), renal anomalies, ID
Del 8q22-q23	*ZFPM2* [5]	Blepharophimosis, widely spaced eyes, epicanthus, flat malar region, thin vermillion of upper lip, downturned corners of mouth, ↓ facial movement	ID w/absent speech, microcephaly, seizures, growth delays [6]
Del 1q41-q42 (OMIM 612530)	*HLX* *DISP* [5]		Limb anomalies (e.g., talipes), cleft lip & palate, seizures, ID
Del 15q24 (OMIM 613406)		Typical craniofacial features	Malformations of hands & feet, growth delays, ID w/marked speech delay
Del 4p16.3 (OMIM 194190)	*FGFRL1* [5]	Typical facial anomalies assoc w/ Wolf-Hirschhorn syndrome	Skeletal anomalies, ID, growth delays
Del 22q11.2		Typical facial anomalies assoc w/ 22q11.2 deletion syndrome, cleft palate	• CHD, skeletal anomalies, hypocalcemia • CDH is present in 0.8% of persons w/22q11 deletion. [7]
Del 17q12		Facial anomalies (See 17q12 Recurrent Deletion Syndrome.)	MODY, cystic renal disease, pancreatic & liver abnormalities, macrocephaly, ID [8]

AD = autosomal dominant; AR = autosomal recessive; CDH = congenital diaphragmatic hernia; CHD = congenital heart defect; ID = intellectual disability; MODY = maturity-onset diabetes of the young

1. See also Congenital Diaphragmatic Hernia Overview.

2. In some persons, only chromosome analysis and/or the inheritance pattern can distinguish between PKS and Fryns syndrome [Veldman et al 2002]. To evaluate for PKS, skin fibroblasts, chorionic 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 or CMA on peripheral blood lymphocytes does not exclude PKS, although CMA may detect PKS when the percentage of tetrasomic cells is relatively high.

3. Izumi & Krantz [2014]

4. Sparse hair is characteristic of PKS, in contrast to Fryns syndrome, in which the sisters originally described by Fryns had low hairlines and hypertrichosis.

5. Yu et al [2020]

6. Kuechler et al [2011]

7. Unolt et al [2017]

8. Goumy et al [2015]

Management

No clinical practice guidelines for Fryns syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual with Fryns syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Fryns Syndrome

System/Concern	Evaluation	Comment
CDH	Chest & abdominal radiographs	
Neurologic	• Cranial US exam to evaluate for structural brain malformations • Neurologic eval & EEG if seizures are suspected • Brain MRI exam	
Eyes	Ophthalmology exam incl fundoscopy	
Cardiovascular	Echocardiogram	
Gastrointestinal	Upper gastrointestinal imaging to evaluate for intestinal malrotation	
Genitourinary	Renal US exam	
Ears/Nose/Throat	Eval w/ENT &/or craniofacial team if cleft palate is suspected	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of Fryns syndrome to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

CDH = congenital diaphragmatic hernia; MOI = mode of inheritance; US = ultrasound

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Fryns Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
CDH	Neonates w/CDH require immediate intubation to prevent inflation of herniated bowel. See also Congenital Diaphragmatic Hernia Overview.	CDH in Fryns syndrome may be amenable to prenatal surgical repair. Survival in a controlled trial of open hysterotomy-guided fetal endoscopic tracheal occlusion vs conventional care was not improved; percutaneous fetal endoluminal tracheal occlusion is still being evaluated [Losty 2014].
Seizures	Standardized treatment w/antiseizure medications by experienced neurologist	
Cataracts / Other ocular anomalies	Management per ophthalmologist	
Congenital heart defects	Management per pediatric cardiologist	
Gastrointestinal malformations	Surgical repair per pediatric gastroenterologist & pediatric surgeon	
Genitourinary malformations	Management per pediatric nephrologist &/or urologist	
Cleft palate	Management per craniofacial team	
Developmental delay	Developmental services as needed incl feeding, motor, adaptive, cognitive, & speech/language	

CDH = congenital diaphragmatic hernia

Surveillance

Table 7. Recommended Surveillance for Individuals with Fryns Syndrome

System/Concern	Evaluation	Frequency
Following successful CDH repair	Evals by pediatric surgeon, nurse specialist, cardiologist, pulmonologist, & nutritionist	As recommended by specialist(s)
Neurologic	Monitor those w/seizures as clinically indicated; assess for new onset of seizures.	At each visit
Development	Monitor developmental progress & educational needs.	
Ocular anomalies	Ophthalmology eval	As needed
Congenital heart defects	Follow up w/cardiologist	
Gastrointestinal malformations	Follow up w/gastroenterologist	
Genitourinary malformations	Follow up w/nephrologist or pediatric urologist	
Cleft palate	Follow up w/craniofacial specialists	

CDH = congenital diaphragmatic hernia

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnancies are managed according to the malformations that have been diagnosed. One literature review concluded that fetoscopic endoluminal tracheal occlusion used as a prenatal interventional strategy can increase survival in cases with severe CDH [Cundy et al 2014], although this technique has most frequently been used for isolated CDH rather than Fryns syndrome.

Therapies Under Investigation

Many different treatments are currently being evaluated for the management of congenital diaphragmatic hernia.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Fryns syndrome caused by pathogenic variants in *PIGN* is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one Fryns syndrome-causing pathogenic variant based on family history).
- If biallelic *PIGN* pathogenic variants have been identified in the proband, molecular genetic testing of the parents is recommended to confirm that both parents are heterozygous for a *PIGN* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- Assuming that both parent are heterozygous for a Fryns syndrome-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with Fryns syndrome have not typically been known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a Fryns syndrome-causing pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives is possible if biallelic *PIGN* pathogenic variants have been identified in an affected family member.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to couples who have had a child with Fryns syndrome and young adults who are at risk of being carriers.
- If the reproductive partner of an individual known to be heterozygous for a *PIGN* pathogenic variant has ancestry from La Réunion or other Indian Ocean islands, they may choose to have carrier screening for a *PIGN* intragenic deletion, which is considered likely to be a founder variant in this population [Alessandri et al 2018].

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

A Priori High-Risk Pregnancy – Sib with Fryns Syndrome

Molecular genetic testing. If biallelic *PIGN* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Ultrasound examination. Fryns syndrome has been diagnosed by two- and three-dimensional ultrasonography and fetal magnetic resonance imaging (MRI). 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 or third trimester, nuchal translucency / cystic hygroma, hyperechogenic bowel, echogenic kidneys, cardiac malformations, 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 can be considered to confirm the presence of a diaphragmatic defect and to search for other anomalies. However, it is possible that Fryns syndrome will be missed during pregnancy without a prior index case [Peron et al 2014].

A Priori High-Risk Pregnancy – Sib with Possible Fryns Syndrome

Chromosome analysis. If the possibility of a chromosomal syndrome associated with CDH and additional major malformations/dysmorphology has not been ruled out in a sib with possible Fryns syndrome, chromosome analysis and CMA of fetal cells may both be warranted.

A Priori Low-Risk Pregnancy – No Family History of Fryns Syndrome

A routine prenatal ultrasound examination may identify a diaphragmatic hernia and/or other malformations raising the possibility of Fryns syndrome in a fetus not known to be at increased risk. In such situations,

chromosome analysis, including karyotype (for evaluation for mosaicism for isochromosome 12p or tetrasomy 12p associated with Pallister-Killian syndrome) and CMA (for other chromosome abnormalities) (see A Priori High-Risk Pregnancy – Sib with Possible Fryns Syndrome) is strongly recommended. Confirmation of the diagnosis of Fryns syndrome, however, may not be possible prior to delivery [Peron et al 2014], pending evaluation with complete physical examination and other imaging studies.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **CDH International**
  Email: info@cdhi.org
  cdhi.org
- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **Helping After Neonatal Death (HAND)**
  PO Box 341
  Los Gatos CA 95031
  Phone: 888-908-HAND (4263)
  www.handonline.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Fryns Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PIGN	18q21.33	GPI ethanolamine phosphate transferase 1	PIGN @ LOVD	PIGN	PIGN

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Fryns Syndrome (View All in OMIM)

229850	FRYNS SYNDROME; FRNS
606097	PHOSPHATIDYLINOSITOL GLYCAN ANCHOR BIOSYNTHESIS CLASS N PROTEIN; PIGN

Molecular Pathogenesis

PIGN is one of a family of proteins responsible for the biosynthesis of glycosylphosphatidylinositol (GPI), which anchors proteins to the outer leaflet of the lipid bilayer of the cell membrane, enabling diverse cellular functions including signal transduction, cell adhesion, and antigen presentation [Brady et al 2014, McInerney-Leo et al 2016, Kinoshita 2020]. *PIGN* encodes GPI-ethanolaminetransferase I (ETI) and transfers EtNP from phosphatidylethanolamine to the 2-position of the first, α4 linked mannose generating

Manα6(EtNP)2Manα4GlcN-(acyl)phosphatidylinositol [Hong et al 1999]. The defective GPI anchor proteins (GPI-APs) caused by pathogenic variants in *PIGN* and other genes involved in GPI anchor biosynthesis result in cellular mislocalization of GPI-APs with subsequent impairment of cell function [Brady et al 2014, Kinoshita 2020]. Aberrant GPI-APs can also disrupt critical developmental pathways such as Wnt signaling, Hedgehog signaling, and BMP signaling [McInerney-Leo et al 2016 and references therein].

Mechanism of disease causation. Fryns syndrome caused by *PIGN* variants is considered to result from loss of function. Pathogenic variants have included intragenic deletions, splice site variants, and frameshift variants predicted to cause premature protein truncation or a null allele.

Table 8. Notable *PIGN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_176787.5 NP_789744.1	c.421dup	p.Ile141AsnfsTer10	Homozygous [Alessandri et al 2018]
	c.694A>T	p.Lys232Ter	Homozygous [McInerney-Leo et al 2016]
NM_176787.5	c.1574+1G>A	--	Homozygous [Brady et al 2014]
	c.1674+1G>C	--	Compound heterozygous [1] [McInerney-Leo et al 2016]
NM_176787.5 NP_789744.1	c.1966C>T	p.Glu656Ter	Compound heterozygous [1] [McInerney-Leo et al 2016]
GRCh37	Chr18:59819870–59824934 deletion [2]	See footnote 3.	Homozygous; likely founder effect in La Réunion & other Indian Ocean islands [Alessandri et al 2018]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. c.[1966C>T]; [c.1674+1G>C]; designation for two variants on two alleles
2. 5.07-kb deletion with breakpoints in exon 5 and intron 7; precise breakpoints unknown (GRCh37/hg19). Using other reference sequences, the designations are *GRCh38:*Chr18:62152637-62157701 and NC_000018.10:g.62152637_62157701del. Listed in ClinVar (VCV000446120.1; accessed 10-4-22).
3. Splicing of deleted allele cannot be predicted; it is predicted to span at least 90 amino acid residues [Alessandri et al 2018].

Chapter Notes

Revision History

- 17 September 2020 (sw) Comprehensive update posted live
- 29 January 2015 (me) Comprehensive update posted live
- 1 June 2010 (me) Comprehensive update posted live
- 18 April 2007 (me) Review posted live
- 8 January 2007 (ams) Original submission

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