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SLC25A24 Fontaine Progeroid Syndrome

Danita Velasco, MD, FAAP, FACMG,[1] Ann Haskins Olney, MD, FACMG,[2] and Lois Starr, MD, PhD, FAAP, FACMG[3]

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Summary

Clinical characteristics

SLC25A24 Fontaine progeroid syndrome is a multisystem connective tissue disorder characterized by poor growth, abnormal skeletal features, and distinctive craniofacial features with sagging, thin skin, and decreased subcutaneous fat suggesting an aged appearance that is most pronounced in infancy and improves with time. Characteristic radiographic features include turribrachycephaly with widely open anterior fontanelle, craniosynostosis, and anomalies of the terminal phalanges. Cardiovascular, genitourinary, ocular, and gastrointestinal abnormalities may also occur. To date, 13 individuals with a molecularly confirmed diagnosis of *SLC25A24* Fontaine progeroid syndrome have been described.

Diagnosis/testing

The diagnosis of *SLC25A24* Fontaine progeroid syndrome is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SLC25A24* identified by molecular genetic testing.

Management

Treatment of manifestations: Management, which is largely symptomatic, may be performed by specialists in multiple disciplines, including a craniofacial clinic (involving plastic surgery, neurosurgery, and otolaryngology), cardiology, pulmonology, gastroenterology, and clinical genetics. Some students may benefit from an individualized education plan through their school.

Surveillance: Routine evaluation to assess development of new manifestations and response to ongoing management.

Author Affiliations: 1 Clinical Geneticist and Assistant Professor, Pediatrics and Munroe-Meyer Institute for Genetics & Rehabilitation University of Nebraska Medical Center Omaha, Nebraska; Email: dvelasco@unmc.edu. 2 Clinical Geneticist and Professor, Pediatrics and Munroe-Meyer Institute for Genetics & Rehabilitation University of Nebraska Medical Center Omaha, Nebraska; Email: aolney@unmc.edu. 3 Clinical Geneticist and Associate Professor, Pediatrics and Munroe-Meyer Institute for Genetics & Rehabilitation University of Nebraska Medical Center Omaha, Nebraska; Email: lstarr@unmc.edu.

Agents/circumstances to avoid: Contact sports and isometric exercise may need to be restricted if cranial anomalies and/or aortic dilatation are present.

Genetic counseling

SLC25A24 Fontaine progeroid syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo* *SLC25A24* pathogenic variant. However, given a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism, prenatal and preimplantation genetic testing may be considered.

Diagnosis

No consensus clinical diagnostic criteria for *SLC25A24* Fontaine progeroid syndrome have been published.

Suggestive Findings

SLC25A24 Fontaine progeroid syndrome **should be suspected** in individuals with the following clinical and radiographic findings.

Clinical findings

- Pre- and postnatal growth failure
- Sagging, thin, and translucent skin with decreased subcutaneous fat, contributing to a progeroid appearance, most pronounced in infancy
- Distinctive craniofacial features (Figure 1). Core features recognizable from infancy include turribrachycephaly, short and downslanted palpebral fissures, depressed nasal root, midfacial retrusion, and small and low-set ears.
- Cranial underossification with large anterior fontanelle (Figure 2), frequently presenting with craniosynostosis
- Sparse scalp hair in infancy with low anterior and posterior hairlines transitioning to coarse, unruly hair with multiple hair whorls (see Figure 1)
- Hypertrichosis of face, back, and extensor surfaces
- Umbilical hernia and underdeveloped abdominal wall musculature (Figure 3)
- Digital anomalies including short distal phalanges, cutaneous syndactyly of fingers or toes, and abnormal nail development (see Figure 3)
- Hypoplastic labia majora in females or cryptorchidism in males

Radiographic findings

- Poorly ossified calvarium (see Figure 2), often with craniosynostosis evident on CT
- Short distal phalanges, with or without cutaneous syndactyly

Establishing the Diagnosis

The diagnosis of *SLC25A24* Fontaine progeroid syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *SLC25A24* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *SLC25A24* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

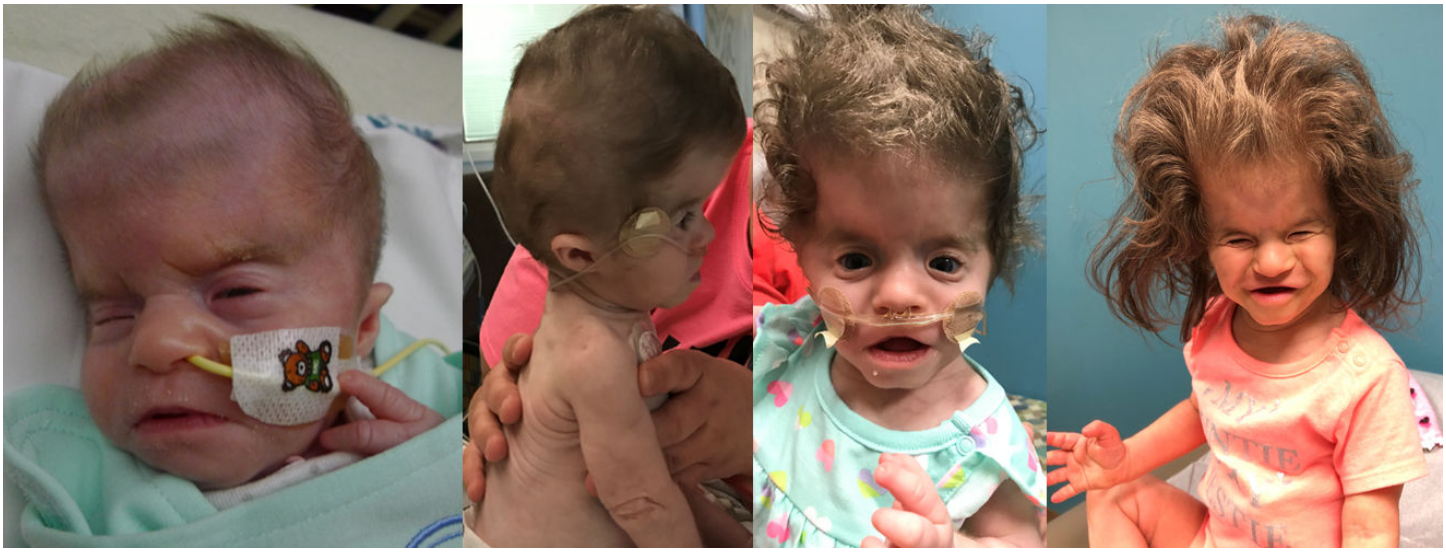

Figure 1. Facial features of female at age six weeks, six months, one year, and 2.5 years. Note turribrachycephaly with broad forehead tapering to a narrower chin and triangular-shaped face. The supraorbital ridges are underdeveloped, and palpebral fissures are typically short and downslanted. Blue or gray sclera have been noted in several individuals. The nasal root is depressed with convex nasal ridge and midface retrusion. Micrognathia in infancy typically develops into relative prognathia with age, and the lower lip and tongue may protrude. Ears are consistently low set and posteriorly rotated with small, dysplastic pinnae. Note evolution of hair pattern, and improved skin appearance over time.

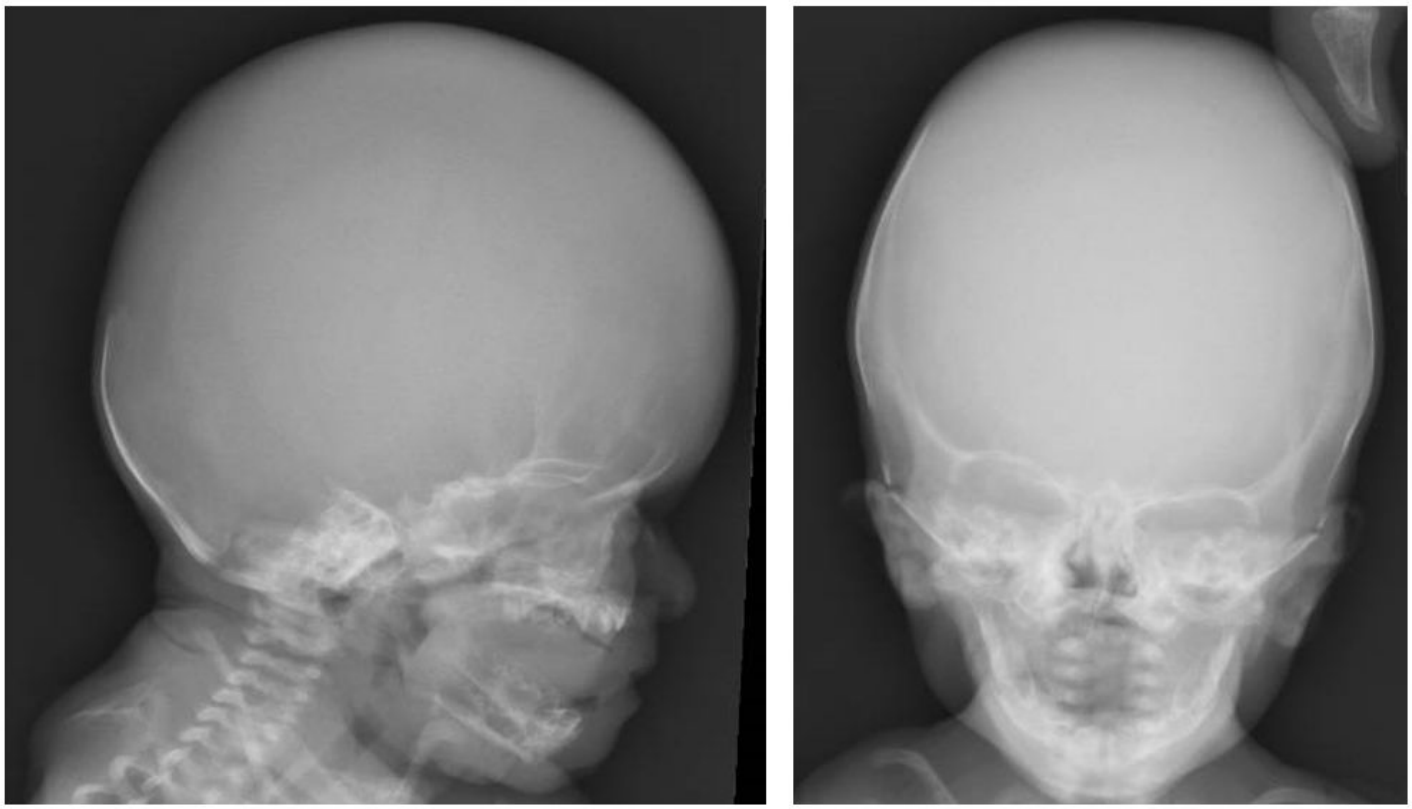

Figure 2. Skull radiographs from the same child at age two weeks. Note nearly absent calvarial ossification.

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).

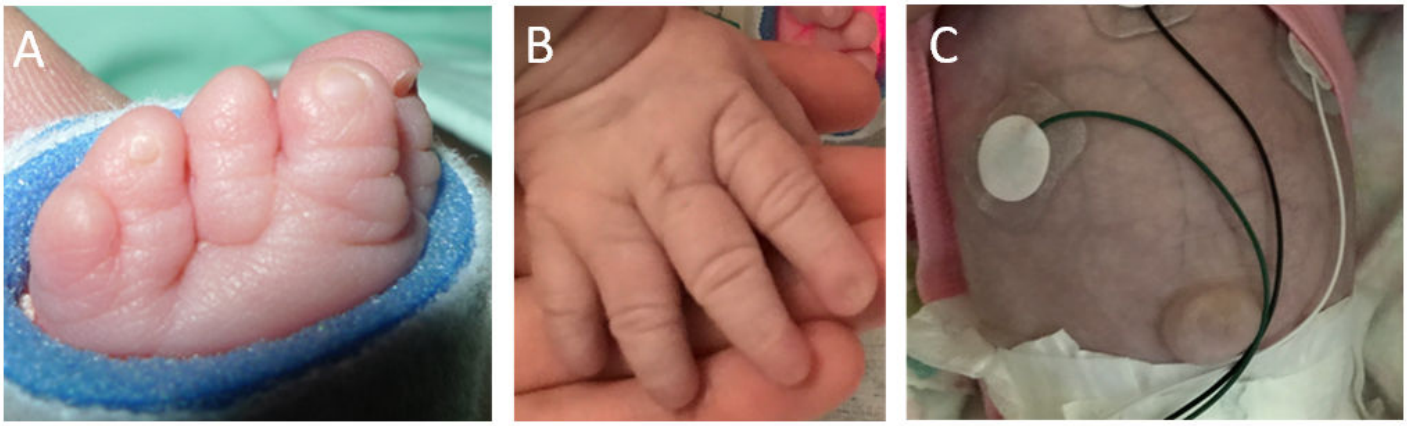

Figure 3. In the same individual at age six weeks (A, B) and six months (C), there is mixed nail dysplasia and aplasia affecting hands and feet (A, B) with syndactyly of the toes and shortened distal phalanges (A, B). Note thin, translucent skin with prominent vessels, lack of subcutaneous fat, and umbilical hernia (C).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *SLC25A24* Fontaine progeroid syndrome has not been considered may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of *SLC25A24* Fontaine progeroid syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SLC25A24* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, if 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; however, to date such variants have not been identified as a cause of this disorder.
- **A craniosynostosis or skeletal disorder multigene panel** that includes *SLC25A24* 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 diagnosis of *SLC25A24* Fontaine progeroid syndrome has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing,** which does not require the clinician to

determine which gene is likely involved, is an option. **Exome sequencing** is most commonly used; **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 *SLC25A24* Fontaine Progeroid Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SLC25A24	Sequence analysis [3]	13/13 [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Ehmke et al [2017]; Writzl et al [2017]; Rodríguez-García et al [2018]; Ryu et al [2019]; Legué et al [2020]; Author, unpublished data
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. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

SLC25A24 Fontaine progeroid syndrome is a multisystem connective tissue disorder characterized by poor growth, abnormal skeletal features, and distinctive craniofacial features with sagging, thin skin and decreased subcutaneous fat suggesting an aged appearance that is most pronounced in infancy and improves with time. Characteristic radiographic features include turribrachycephaly with widely open anterior fontanelle, craniosynostosis, and anomalies of the terminal phalanges. Cardiovascular, genitourinary, ocular, and gastrointestinal abnormalities may also occur.

Prior to identification of the molecular basis of this disorder, clinical findings were published by Gorlin et al [1960], Fontaine et al [1977], and Petty et al [1990]. Subsequent published case reports noted significant clinical overlap particularly with "Petty syndrome" and "Fontaine-Farriaux syndrome" [Castori et al 2009, Braddock et al 2010, Writzl et al 2017]. To date, 13 individuals have been described with a molecularly confirmed diagnosis of *SLC25A24* Fontaine progeroid syndrome [Ehmke et al 2017; Writzl et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data]. The clinical findings discussed in this section are based on these reports (see Table 2).

Note: (1) Of the four individuals with an *SLC25A24* pathogenic variant included in the report by Writzl et al [2017], three had previously been reported: Patient 2 in Faivre et al [1999], Patient 3 in Rodríguez et al [1999], and Patient 4 in Castori et al [2009]. (2) Of the five females with an *SLC25A24* pathogenic variant and clinical findings suggestive of Gorlin-Chaudhry-Moss syndrome included in the report by Ehmke et al [2017], one (Patient 4) had previously been reported by Adolphs et al [2011].

Table 2. Select Features of *SLC25A24* Fontaine Progeroid Syndrome

Feature	Proportion of Persons w/Feature [1]	Comment
Pre- & postnatal growth failure	12/13	Poor weight gain is universal; short stature is observed in most persons.
Abnormal skull	13/13	• Turribrachycephaly or brachycephaly (12/12) • Large anterior fontanelle (10/12) • Craniosynostosis (9/10)
Characteristic craniofacial features	13/13	See Figure 1.
Ocular anomalies	10/10	Incl microphthalmia, hyperopia, eyelid anomalies, & blue or gray sclera
Sagging, thin, translucent skin	12/12	
Hypertrichosis	10/10	Involving face, back, & extensor surfaces of arms & legs
Skeletal anomalies	13/13	• Short distal phalanges (11/13) • Syndactyly (7/13) • Nail aplasia/hypoplasia (12/13) • Platyspondyly (2/13) • Hip dysplasia (1/13) • Delayed bone age (1/13)
Cardiovascular anomalies	9/11	• Structural abnormalities (5/11) • Pulmonary hypertension (4/10) • Aortic dilatation (6/11) • Type A aortic dissection (1/11)
External genital anomalies	11/12	• 8/9 females w/labial hypoplasia • 3/3 males w/cryptorchidism
Developmental delay w/normal cognition	7/8	• Delayed acquisition of milestones, particularly motor skills, is common. • In school-aged children, normal academic progress was reported in 7/8.

1. 11 survived >24 hours.

Growth

Prenatal growth. All but one affected individual presented with intrauterine growth restriction [Ehmke et al 2017]. Oligohydramnios is also commonly noted in the third trimester.

Z scores for birth weight ranged from -1 to -4.7, for birth length from +0.1 to -4, and for head circumference from -1.4 to -5.

Postnatal growth. Poor weight gain was observed in all individuals who lived more than 24 hours. Z scores for weight at time of last evaluation ranged from -2.7 to -6.

Feeding problems in infancy with poor growth are common. Three individuals have required gastrostomy feeds for poor feeding and/or reflux with aspiration [Ehmke et al 2017; Author, unpublished data].

Short stature was present in nine of 11 individuals who lived more than 24 hours, showing poor linear growth with Z scores ranging from -1.2 to -6.

Microcephaly, proportionate to height, is frequently present.

Craniofacial Features

Turribrachycephaly or brachycephaly is apparent at birth in most individuals and may be noted prenatally. In all but two individuals for whom there are detailed infant records, large anterior fontanelle is present. In the 11

individuals who lived longer than the neonatal period, craniosynostosis (most often involving the coronal sutures) was confirmed in nine and suspected in another.

Skin and Hair

Excessively wrinkled, sagging, and thin skin is typically noted at birth. Dermal translucence with prominent vasculature and decreased subcutaneous fat is common. In combination these skin findings (reflecting an apparent lipodystrophy) contribute to a progeroid appearance in infancy that improves with time.

The hair pattern is distinctive. Hypertrichosis, most frequently over the back, neck, and face, is present at birth and persists at least through childhood. In neonates, sparse frontotemporal scalp hair with low anterior and posterior hairlines are frequently noted. With age, scalp hair becomes coarse and abnormal hair whorls and growth patterns are common (see Figure 1).

Skeletal

Digital abnormalities, present in all reported individuals, include a mix of short distal phalanges (11/13), cutaneous syndactyly (7/13), and nail aplasia or hypoplasia (12/13) [Ehmke et al 2017; Writzl et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data]. Radiographs show shortened distal phalanges.

Mixed nail hypoplasia and aplasia may be present on some digits; normal nails may be present on other digits. Postaxial digits of hands and feet tend to be more severely affected than preaxial digits.

Cutaneous syndactyly of hands or feet was present in seven individuals; in the six for whom it was specified, syndactyly involved toes 2-3 and 4-5 (in 2 individuals) [Ehmke et al 2017; Author, unpublished data], toes 2-3 only (1 individual), toes 4-5 only (1 individual) [Ehmke et al 2017, Legué et al 2020], fingers 3-4 only (1 individual), and fingers 4-5 only (1 individual) [Writzl et al 2017, Ryu et al 2019].

Other skeletal findings have been variably reported and include the following:

- Platyspondyly in two infants [Castori et al 2009; Author, unpublished]
- Nonspecific long bone diaphyseal and ossification abnormalities in one infant [Rodríguez et al 1999]
- Congenital hip dysplasia in one individual [Rodríguez-García et al 2018]
- Delayed bone age in one individual [Adolphs et al 2011]

Cardiovascular

Congenital heart defects (patent ductus arteriosus, atrial septal defect secundum, bicuspid aortic valve, and dysplastic valves) occurred in four individuals [Ehmke et al 2017, Writzl et al 2017].

Pulmonary hypertension occurred in four individuals during infancy [Ehmke et al 2017; Writzl et al 2017; Author, unpublished data].

Two had normal neonatal echocardiograms and developed pulmonary hypertension before age six months [Writzl et al 2017; Author, unpublished data].

Gastroesophageal reflux and aspiration requiring fundoplication and gastrostomy tube occurred in at least two individuals who also developed pulmonary hypertension [Ehmke et al 2017; Author, unpublished data]. In at least one individual, right heart pressure improved following gastric fundoplication [Author, unpublished data].

Aortic dilatation was seen in six of the 11 individuals who lived more than 24 hours. Aortic dilatation, which had not been present on neonatal echocardiograms, developed in at least three individuals who did not have other cardiac anomalies [Ehmke et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data]. In one individual dilatation progressed during treatment with atenolol [Rodríguez-

García et al 2018]. Another individual presented with an ascending aortic dissection at age 45 years [Legué et al 2020].

Development

Delayed acquisition of milestones in infancy is common. Normal cognition has been described in individuals living beyond early childhood.

Specific details regarding acquisition of developmental milestones are limited to four individuals in whom independent sitting was achieved at 12-18 months, walking at 19-36 months, and speech at 16-24 months [Ehmke et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Author, unpublished data].

Other

Central nervous system

- Two individuals had hydrocephalus requiring shunt placement [Ehmke et al 2017]; these were the only individuals with relative macrocephaly compared to height.
- Two individuals had brain malformations: one with thin corpus callosum, ventriculomegaly, dysplastic cerebella vermis, pineal gland cyst, and large retrocerebellar area [Ehmke et al 2017]; and one with gyral simplification consistent with pachygyria, cerebellar hypoplasia, and subependymal heterotopia noted on autopsy [Writzl et al 2017].
- Five others had no abnormalities on brain imaging (MRI or CT) [Ehmke et al 2017; Writzl et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Author, unpublished data].

Ocular

- Hyperopia is common in individuals older than age one year [Ehmke et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data].
- Microphthalmia was present in several individuals [Rodríguez-García et al 2018, Ryu et al 2019, Legué et al 2020].
- One infant had iridocorneal adhesions and corneal clouding at birth [Writzl et al 2017].

Conductive hearing loss was present in six of eight individuals; at least one required myringotomy tubes for chronic middle ear effusion [Ehmke et al 2017; Writzl et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data].

Dentition

- Oligodontia, microdontia, and hypodontia have been reported.
- Primary dentition may be normal despite subsequent abnormalities of the permanent teeth [Ehmke et al 2017, Ryu et al 2019, Legué et al 2020].

Abdomen/gastrointestinal

- Umbilical hernia with diastasis recti or hypoplasia of abdominal musculature was present in 11 of 13 individuals [Ehmke et al 2017; Writzl et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data]. One individual had repair of umbilical hernia with subsequent recurrence [Ryu et al 2019].
- Intestinal malrotation was identified at autopsy in one infant [Writzl et al 2017].

Genital

- Hypoplastic labia were reported in 8 of 10 females [Ehmke et al 2017; Writzl et al 2017; Rodríguez-García et al 2018; Ryu et al 2019; Legué et al 2020; Author, unpublished data].

- Cryptorchidism was present in all three reported males. One also had micropenis [Writzl et al 2017] and one had hypospadias and cryptorchidism [Rodríguez-García et al 2018].

Severe and frequently life-limiting infections have been reported in six individuals [Ehmke et al 2017; Writzl et al 2017; Author, unpublished data]. In two of these individuals, persistent leukocytosis was also present [Writzl et al 2017; Author, unpublished data].

Prognosis

It is unknown whether life span in *SLC25A24* Fontaine progeroid syndrome is abnormal. One individual with a molecularly confirmed diagnosis is alive at age 45 years, demonstrating that survival into adulthood is possible [Legué et al 2020].

Additionally, earlier reports of individuals clinically diagnosed with Gorlin-Chaudhry-Moss syndrome and Petty syndrome included individuals in their 30s and 40s [Petty et al 1990, Ippel et al 1992]. Since many adults with disabilities or malformations have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified. All individuals have a similar substitution at residue 217 (p.Arg217His or p.Arg217Cys) with no significant difference in clinical presentation (see Table 7).

Nomenclature

The following designations, previously thought to represent discrete phenotypes, were consolidated under the name "*SLC25A24* Fontaine progeroid syndrome" following identification of their shared molecular etiology in 2017 [Ehmke et al 2017, Writzl et al 2017]:

- Hutchinson-Gilford progeria-like syndrome [Faivre et al 1999, Rodríguez et al 1999, Writzl et al 2017]
- Fontaine-Farriaux syndrome [Castori et al 2009, Writzl et al 2017]
- Gorlin-Chaudhry-Moss syndrome [Adolphs et al 2011, Ehmke et al 2017]

Although to date no individual with a clinical diagnosis of Petty syndrome has been confirmed to have a pathogenic variant in *SLC25A24*, the remarkably similar clinical features have led multiple authors to propose a shared etiology [Castori et al 2009, Braddock et al 2010, Writzl et al 2017, Ryu et al 2019].

Prevalence

The prevalence is unknown. To date, 13 individuals with molecularly confirmed *SLC25A24* Fontaine progeroid syndrome have been reported worldwide.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC25A24*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *SLC25A24* Fontaine Progeroid Syndrome

Gene(s)	DiffDx Disorder	MOI	Key Overlapping Clinical Features of DiffDx Disorder	Distinguishing Clinical Features of DiffDx Disorder
ALDH18A1	De Barsy syndrome A (ARCL3A) (OMIM 219150)	AR	Postnatal growth restriction, wrinkled, sagging, & translucent skin w/prematurely aged appearance, enlarged fontanelles, downslanted palpebral fissures, umbilical hernia, dilatation of aortic root, DD	Cortical & cerebellar brain malformations, prominent ears, cataracts, adducted thumbs, abnormal tone, ID
ALDH18A1	ADCL3 (OMIM 616603)	AD	Postnatal growth restriction, wrinkled, sagging, & translucent skin w/prematurely aged appearance, hernias, late fontanelle closure	Cataracts, cranial vessel tortuosity, ID
ATP6V0A2	*ATP6V0A2*-related cutis laxa (ARCL2A)	AR	Growth restriction; delayed closure of fontanelles; thin, winkled, & sagging skin; downslanted palpebral fissures; hearing loss	Neuronal migration anomalies, abnormal TIEF & apoC-III screening (CDG)
COG4	Saul-Wilson syndrome	AD	Pre- & postnatal growth restriction, large fontanelle w/delayed closure, prominent scalp veins, triangular face, short distal phalanges, DD w/normal cognition	Characteristic skeletal malformations, cataracts, & retinal anomalies
EFEMP2	*EFEMP2*-related cutis laxa	AR	Thin, translucent skin, umbilical/inguinal hernias, micrognathia/retrognathia, dysplastic ears, aortic aneurysms, pulmonary hypertension	Arterial stenosis, diaphragmatic abnormalities, emphysema arachnodactyly
LMNA	Hutchinson-Gilford progeria syndrome	AD	Postnatal growth restriction, triangular face, ↓ subcutaneous fat, acquired nail dystrophy	Absence of prenatal growth restriction, sclerodermatous skin changes, partial-to-total alopecia, digital acro-osteolysis
POLR3A	Wiedemann-Rautenstrauch syndrome (See POLR3-Related Leukodystrophy.)	AR	Severe pre- & postnatal growth restriction, wide-open fontanelle, generalized lipodystrophy, prominent scalp veins, aged appearance in infancy	Natal teeth, no distal limb anomalies, sparse scalp hair, ID
PYCR1	ARCL2B (OMIM 612940)	AR	Postnatal growth restriction, wide fontanelles, prominent forehead, thin, wrinkled, sagging, & translucent skin, sunken eyes w/short palpebral fissures	ID
PYCR1	De Barsy syndrome B (ARCL3B) (OMIM 614438)	AR	Postnatal growth restriction, wrinkled, sagging, & translucent skin w/prematurely aged appearance, hernias, late fontanelle closure	Movement disorder, athetoid movements, cataracts, ID
ZMPSTE24	Mandibuloacral dysplasia w/ type B lipodystrophy (OMIM 608612)	AR	Postnatal growth restriction, delayed closure of cranial sutures, generalized lipodystrophy, prominent vasculature	Acro-osteolysis of phalanges, dysplastic clavicles, severe mandibular dysplasia, sometimes focal sclerosing glomerulosclerosis

AD = autosomal dominant; apoC-III = apolipoprotein C-III; AR = autosomal recessive; CDG = congenital disorders of glycosylation; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; TIEF = transferrin isoelectrofocusing

Management

No clinical practice guidelines for *SLC25A24* Fontaine progeroid syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SLC25A24* Fontaine progeroid syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SLC25A24* Fontaine Progeroid Syndrome

System/Concern	Evaluation	Comment
Cardiovascular	Eval by cardiologist & echocardiogram	Assess for pulmonary hypertension, aortic dilatation, & ↑ risk of dissection.
Skeletal	Cranial CT & osseous survey	Assess for cranial suture synostosis; monitor cranial ossification & vertebral & digital anomalies.
Ocular	Eval by ophthalmologist	Assess for ocular, eyelid, & vision anomalies.
Feeding/ Gastrointestinal	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube & fundoplication in persons w/dysphagia &/or aspiration risk.
Dental	Routine eval upon tooth eruption	Assess for oligodontia, microdontia, & malocclusion.
Hearing	Hearing eval	Risk for conductive hearing loss
Genital	Assess for external genital anomalies.	Referral to urologist as clinically indicated to treat cryptorchidism &/or hypospadias
CNS	Consider brain MRI.	Rarely brain malformations / hydrocephalus are present.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / need for IEP
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SLC25A24* Fontaine progeroid syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

IEP = individualized education plan; MOI = mode of inheritance

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

Treatment of Manifestations

Management, which is largely symptomatic, may be performed by specialists in multiple disciplines, including a craniofacial clinic (involving plastic surgery, neurosurgery, and otolaryngology), cardiology, pulmonology, gastroenterology, and clinical genetics. Some students may benefit from an individualized education plan (IEP) through their school.

Table 5. Treatment of Manifestations in Individuals with *SLC25A24* Fontaine Progeroid Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Craniosynostosis / Underossified skull	Mgmt in multidisciplinary craniofacial clinic is recommended.	• W/ossification of skull, craniosynostosis may become apparent. • Protective helmet may be considered w/delayed ossification.
Pulmonary hypertension	Multidisciplinary care w/providers familiar w/mgmt of pulmonary hypertension	• Mgmt of microaspiration & oxygen therapy help. • Consider sleep study (particularly in persons w/midfacial retrusion).
Aortic dilatation	Tertiary cardiovascular care	• Aneurysm w/dissection has been reported at aortic root & not elsewhere in arterial tree. • Dissection may occur at smaller aortic diameters.
Hearing loss	Per treating ENT/audiologist	Myringotomy tubes if persistent middle ear effusions are present
Umbilical hernia	Surgical repair if persistent	
Developmental delay	See Developmental Delay Management Issues.	Cognition is typically in normal range despite early delay in acquisition of milestones.

Developmental Delay Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Surveillance

Table 6. Recommended Surveillance for Individuals with *SLC25A24* Fontaine Progeroid Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measure height, weight, & head circumference	At each visit
Cardiovascular (pulmonary hypertension, aortic dilatation)	• Echocardiogram & eval by cardiologist • Angiography may be indicated.	• At diagnosis & then based on individual findings • Echocardiography at least every 3 yrs
Hearing	Routine audiologic eval indicated	Annually or per treating ENT
Ocular	Routine ophthalmologic eval	Annual assessment or per treating ophthalmologist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Family/ Community	Assess family need for social work support (e.g., home nursing, other local resources) & care coordination or follow-up genetic counseling if new questions arise (e.g., family planning).	

Agents/Circumstances to Avoid

Contact sports and isometric exercise may need to be restricted if cranial anomalies and/or aortic dilatation are present. Note, in the absence of severe aortic dilatation or other clinical restriction, aerobic activity is encouraged.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

SLC25A24 Fontaine progeroid syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. All probands reported to date whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo SLC25A24* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *SLC25A24* Fontaine progeroid syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo SLC25A24* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present only in the germ cells.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the *SLC25A24* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *SLC25A24* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Individuals with *SLC25A24* Fontaine progeroid syndrome are not known to reproduce and fertility has not been assessed.

Other family members. Given that all probands with *SLC25A24* Fontaine progeroid syndrome reported to date have the disorder as a result of a *de novo SLC25A24* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo SLC25A24* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org

- **FACES: National Craniofacial Association**
  Phone: 800-332-2373; 423-266-1632
  Email: info@faces-cranio.org
  www.faces-cranio.org

- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs

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. SLC25A24 Fontaine Progeroid Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC25A24	1p13.3	Mitochondrial adenyl nucleotide antiporter SLC25A24	SLC25A24 database	SLC25A24	SLC25A24

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 SLC25A24 Fontaine Progeroid Syndrome (View All in OMIM)

608744	SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL CARRIER, PHOSPHATE CARRIER), MEMBER 24; SLC25A24
612289	FONTAINE PROGEROID SYNDROME; FPS

Molecular Pathogenesis

SLC25A24 encodes calcium-binding mitochondrial carrier protein SCaMC-1. A calcium-sensitive N-domain regulatory region that is followed by six transmembrane helices forms an inner mitochondrial transmembrane domain that (1) regulates the intramembranous adenine pool via transporting adenine nucleotides in exchange for phosphate [Palmieri et al 2020] and (2) may play a role in resistance to oxidative stress by contributing to formation of the mitochondrial permeability transition pore [Ehmke et al 2017].

Knockdown of SLC25A24 contributes to the oxidative stress and calcium overload and increases susceptibility to mitochondrial permeability transition pore-dependent cell death [Traba et al 2012].

Mechanism of disease causation. The specific mechanism by which *SLC25A24* variants result in the multisystem clinical features of *SLC25A24* Fontaine progeroid syndrome is unclear.

Pathogenic variants causative of Fontaine progeroid syndrome have been restricted to codon 217 in exon 5 of *SLC25A24*. This position is in the transmembrane domain, located at the end of the predicted helix 1. The Arg217 residue is part of the conserved mitochondrial carrier family motif, with substitutions to this residue expected to narrow the substrate cavity [Writzl et al 2017]. Mitochondrial fragmentation and swelling in response to oxidative stress in cells expressing missense variants supports a gain-of-function effect, interfering with regulation of the mitochondrial permeability transition pore [Ehmke et al 2017].

***SLC25A24*-specific laboratory technical considerations.** Pathogenic variants causative of Fontaine progeroid syndrome have been restricted to codon 217 in exon 5 of *SLC25A24*. See Table 7.

Table 7. Notable *SLC25A24* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_013386.5 NP_037518.3	c.649C>T	p.Arg217Cys	Recurrent pathogenic variants [Ehmke et al 2017, Writzl et al 2017, Rodríguez-García et al 2018, Ryu et al 2019]
	c.650G>A	p.Arg217His	

Variants listed in the table have been provided by the authors. *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.

Chapter Notes

Revision History

- 9 June 2022 (bp) Review posted live
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