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MYRF-Related Cardiac Urogenital Syndrome

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Summary

Clinical characteristics

MYRF-related cardiac urogenital syndrome (*MYRF*-CUGS) is primarily characterized by anomalies of the internal and external genitalia, congenital heart defects, and eye anomalies. 46,XY individuals can have a range of anomalies of the genitalia, from isolated unilateral cryptorchidism to ambiguous genitalia to typical-appearing female genitalia. 46,XX individuals can have atypical internal genitalia including absent uterus, absent fallopian tubes, small or absent ovaries, absent vagina, or blind-ending vagina. A number of congenital heart defects have been described, with scimitar syndrome being the most common. Eye issues, present in a vast majority of affected individuals, include high hyperopia and nanophthalmos (an ocular malformation featuring short axial length due to small anterior and posterior segments with thickened choroid and sclera and normal lens volume). Because of the common nature of the eye anomalies, it has been suggested that this condition may be more accurately referred to as "*MYRF*-related ocular cardiac urogenital syndrome." Other features of the condition include a broad range of developmental delay /intellectual disability (DD/ID), from typical development and cognition to severe DD/ID; pulmonary abnormalities and diaphragmatic issues (congenital diaphragmatic hernia / diaphragmatic eventration); intestinal malrotation; and mild growth and feeding problems.

Diagnosis/testing

The diagnosis of *MYRF*-CUGS is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MYRF* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for differences of sex development (DSD) conditions, including hormone therapy, psychosocial support, gender identity assessment, and surgical intervention (e.g., orchidopexy and/or hypospadias repair); thyroid replacement therapy for hypothyroidism; standard treatment of refractive

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error, nanophthalmos, DD/ID, congenital heart defects, diaphragmatic defects, pulmonary hypoplasia, intestinal malrotation, splenic anomalies, and renal anomalies.

Surveillance: Measurement of growth parameters, assessment of developmental progress and educational needs, and monitoring for respiratory insufficiency at each visit; at least annual ophthalmic evaluations; monitoring for onset and progression of puberty at each visit from around age seven years until puberty is complete; assessment of mood, libido, energy, erectile function, acne, breast tenderness, and presence or progression of gynecomastia at each visit in undervirilized 46,XY adolescents and adults; DXA scan in individuals with DSD every three to five years after puberty, or annually if osteopenia is identified. For those on testosterone replacement therapy, measurement of serum testosterone levels at three-month intervals to help establish an optimal dose with subsequent annual measurements; measurement of hematocrit, prostate-specific antigen level, and digital rectal exam three, six, and 12 months after initiation of testosterone therapy and then annually; lipid profile and liver function tests annually.

Agents/circumstances to avoid: Hormone replacement therapy in those with hormone-responsive cancers; oral androgens (e.g., methyltestosterone or fluoxymesterone) for long-term therapy due to liver toxicity.

Genetic counseling

MYRF-CUGS is inherited in an autosomal dominant manner. Many affected individuals reported to date have the disorder as the result of a *de novo MYRF* pathogenic variant. Each child of an individual with *MYRF*-CUGS has a 50% chance of inheriting the *MYRF* pathogenic variant. Manifestations within a family are highly variable, and offspring may have significantly more or fewer manifestations than the proband. Once the *MYRF* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *MYRF*-related cardiac urogenital syndrome (*MYRF*-CUGS) have been published.

Suggestive Findings

MYRF-CUGS **should be suspected** in individuals with any of the following clinical, imaging, and family history findings.

Clinical findings

- Ambiguous genitalia, micropenis, hypospadias, and/or cryptorchidism in 46,XY individuals or müllerian anomalies in 46,XX individuals
- Eye anomalies including high hyperopia and nanophthalmos
- Congenital heart defects including hypoplastic left heart or scimitar syndrome (partial or total anomalous pulmonary venous return of the right lung to the inferior vena cava with dextroposition of the heart, right lung and pulmonary artery hypoplasia, and anomalous systemic blood supply to the lung)
- Congenital diaphragmatic hernia
- Pulmonary hypoplasia, even in the absence of a diaphragmatic abnormality

Imaging findings

- Hypoplasia or aplasia of ovaries and/or müllerian structures in 46,XX individuals
- Presence of müllerian structures in 46,XY individuals
- Intestinal malrotation

Family history. Most probands with *MYRF*-CUGS reported to date have a *de novo* pathogenic variant, and thus represent a simplex case (i.e., a single occurrence in a family). Occasionally, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). The presentation can be extremely variable and parents may be very mildly affected.

Establishing the Diagnosis

The diagnosis of *MYRF*-CUGS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *MYRF* 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 a heterozygous *MYRF* 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 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 *MYRF*-CUGS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of *MYRF*-CUGS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *MYRF* 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 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 differences of sex development, congenital heart disease, or congenital diaphragmatic hernia multigene panel** that includes *MYRF* 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. Because *MYRF*-CUGS is a relatively newly recognized condition, multigene panels often do not include this gene. (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 *MYRF*-CUGS has not been considered because an individual has atypical or subtle phenotypic features, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **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 *MYRF*-Related Cardiac Urogenital Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MYRF	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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.

Clinical Characteristics

Clinical Description

To date, 54 individuals with *MYRF*-related cardiac urogenital syndrome (*MYRF*-CUGS) (more than 20 unpublished, and 32 published plus an extremely large multiplex family) have been identified with a pathogenic variant in *MYRF* [Authors, personal observation; Chitayat et al 2018; Pinz et al 2018; Qi et al 2018; Garnai et al 2019; Guo et al 2019; Hamanaka et al 2019; Rossetti et al 2019; Siggs et al 2019; Xiao et al 2019; Globa et al 2022; Gupta et al 2022]. The following description of the phenotypic features associated with *MYRF*-CUGS is based on these reports.

Table 2. *MYRF*-Related Cardiac Urogenital Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Genital anomalies (internal &/or external)	32/36 (89%)	Genital anomalies can be present in both 46,XX & 46,XY persons.
Eye anomalies	16/19 (84%)	High hyperopia or nanophthalmos are predominant.
Developmental delay / intellectual disability	15/20 (75%)	When present, can range from mild speech delay only to ID (lowest reported IQ: 63) [1]
Congenital heart defects	26/38 (68%)	
Congenital diaphragmatic hernia	15/48 (31%)	Some affected persons have diaphragmatic eventration.
Primary pulmonary hypoplasia	10/33 (30%)	Of 33 persons who did NOT have CDH, 10 had pulmonary hypoplasia.

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Gastrointestinal issue	5 affected persons	3 w/intestinal malrotation, 2 w/splenic anomalies

CDH = congenital diaphragmatic hernia; ID = intellectual disability; IQ = intelligence quotient
1. Normal IQ level is considered greater than or equal to 70.

Variations in genitalia may be the only finding in an individual with *MYRF*-CUGS and manifestations may be subtle.

- **46,XY individuals.** The majority of reported individuals have a 46,XY karyotype. The genitourinary anomalies are very broad and range from isolated unilateral cryptorchidism to typically appearing female genitalia. Common physical findings may include micropenis, hypospadias, chordee, small testes, bifid scrotum, and/or persistent urachus. Müllerian structures including uterus and vagina (typically hypoplastic) may be present. Consistent with the full spectrum of nonbinary (ambiguous) genitalia, some individuals have varying degrees of testicular dysgenesis including Sertoli and/or Leydig cell hyperplasia, paucity of germ cells, tubular atrophy, and decreased fertility / infertility [Hamanaka et al 2019, Globa et al 2022, Gupta et al 2022].
- **XX individuals.** Only six affected individuals have been reported with a 46,XX chromosomal complement. Of these, three had atypical internal genitalia, including absent uterus, fallopian tubes, small or absent ovaries, absent vagina, or blind-ending vagina.

Ophthalmic involvement. Of 19 individuals with well described and deeply evaluated eye morphology, 16 had high hyperopia (farsightedness). Some were evaluated because of clinical concerns, and some were seen because of their *MYRF*-CUGS diagnosis. Some were ascertained from cohorts of individuals with nanopthalmos, so this particular finding may be an overestimate. These 19 individuals do not include the family reported by Garnai et al [2019], nor do they include an additional large multiplex family that had ocular phenotyping only, as these individuals may have the ocular-limited allelic condition (see Genetically Related Disorders). Overall, nanopthalmos / high hyperopia appears to be one of the most common features of *MYRF*-CUGS (see Genotype-Phenotype Correlations).

Nanophthalmos is associated with secondary complications including amblyopia, esotropia, angle closure glaucoma, and spontaneous and postsurgical choroidal effusions [Carricondo et al 2018]. Peripheral chorioretinal scarring and mild retinal pigment epithelial mottling have been reported in some affected individuals and may represent a primary finding in individuals with *MYRF*-CUGS as opposed to sequela of nanophthalmos [Garnai et al 2019, Hagedorn et al 2020].

Developmental delay (DD) and intellectual disability (ID). There is a broad range of DD/ID from typical development and cognition to severe developmental delay and intellectual disability. Severity and rates of intellectual disability or delayed developmental milestones may be affected by cardiopulmonary defects. Of the 15 individuals who had DD/ID:

- Three had speech delay;
- Eight had global delays or severe delay (7 of the 8 had cardiopulmonary issues that required extensive hospitalizations and surgeries);
- Of individuals without cardiopulmonary malformations, only one was reported with a developmental disorder, in this case autism spectrum disorder.

Cardiovascular anomalies. The spectrum of cardiovascular anomalies is broad, ranging from isolated dextrocardia to hypoplastic left heart syndrome. Scimitar syndrome (see Suggestive Findings) is also commonly reported. Other congenital heart defects that have been reported:

- Atrial septal defect
- Ventriculoseptal defect
- Aortic arch hypoplasia
- Coarctation of the aorta
- Bicuspid aortic valve
- Aortic atresia
- Mitral valve atresia
- Tetralogy of Fallot

Pulmonary abnormalities and diaphragmatic issues. Of deeply phenotyped individuals, approximately half have either congenital diaphragmatic hernia (CDH) or pulmonary hypoplasia without CDH. CDH can be left-sided or right-sided, with left-sided predominance. Diaphragmatic eventration has also been reported.

Gastrointestinal issues. Although not a prominent feature, three individuals have been reported with intestinal malrotation [Chitayat et al 2018; Authors, personal observation].

- There are further reports of affected individuals having gastroesophagal reflux disease, poor feeding, and G-tube dependence, although some of these issues may be secondary to cardiopulmonary disease.
- One individual had an accessory spleen [Qi et al 2018] and another had a cleft spleen [Pinz et al 2018].
- There has also been one report of a 46,XY individual with hepatotesticular fusion and splenotesticular fusion [Chitayat et al 2018] and one individual with appendiculo-umbilical fistula [Author, personal observation].

Growth/feeding

- One individual is reported to have short stature [Qi et al 2018]; intrauterine growth restriction was found in another individual [Authors, personal observation].
- Microcephaly has been observed in three affected individuals [Authors, personal observation].
- Poor feeding, which may be secondary to neurologic issues and the effects of severe cardiopulmonary disease, has also been reported.

Dysmorphology. The majority of reported individuals who were evaluated have no recognizable dysmorphic features. Widely spaced eyes have been observed in three affected individuals [Chitayat et al 2018; Author, personal observation].

Other rarely reported features. The following have been reported in a few known affected individuals to date. It is unclear if these findings are rare features of *MYRF*-CUGS or rare co-occurrences of two unrelated findings.

- **Neurologic findings**
  - Hypotonia has been reported in three affected individuals.
  - One individual with an autism spectrum disorder diagnosis has been reported; this individual had no major cardiopulmonary disease.
  - One individual who underwent brain MRI had a posterior fossa cyst [Hagedorn et al 2020].
  - Two affected individuals had delayed myelination patterns noted on brain MRI.
- **Endocrinologic.** One affected individual had thymic fibrosis and involution [Pinz et al 2018], and another had hypothyroidism [Authors, personal observation].
- **Renal.** One affected individual with a horseshoe kidney with associated hydronephrosis has been reported [Rossetti et al 2019].

Genotype-Phenotype Correlations

Large families with nanophthalmos as the predominant feature have been found to harbor pathogenic variants that are predicted to alter or truncate the C terminus of the MYRF protein (see Genetically Related Disorders);

however, it is unclear how comprehensively these individuals were evaluated for other features of *MYRF*-CUGS. It is unknown if these pathogenic variants cause only an ocular phenotype or if they predispose to the ocular findings in individuals with *MYRF*-CUGS.

- The *MYRF* splice site pathogenic variant c.3376-1G>A has been associated with nanophthalmos [Garnai et al 2019]. Four of 41 sampled individuals in the large family with this pathogenic variant have cardiac defects.
- Truncating/altering C-terminal pathogenic variants (splicing or single-base deletion) predispose to autosomal dominant high hyperopia and nanophthalmos [Garnai et al 2019, Guo et al 2019, Siggs et al 2019].

Nomenclature

Because nanopthalmos /high hyperopia appears to be one of the most common features in *MYRF*-CUGS, the authors suggest that the disorder be referred to as *MYRF*-related ocular cardiac urogenital syndrome or *MYRF*-OCUGS.

Prevalence

The prevalence of *MYRF*-CUGS is unknown; it has been identified in more than 56 individuals.

Genetically Related (Allelic) Disorders

Nanophthalmos/hyperopia. It is unclear whether certain pathogenic variants in *MYRF* can lead to isolated nanophthalmos/hyperopia without other features of *MYRF*-related cardiac urogenital syndrome (*MYRF*-CUGS) (see Genotype-Phenotype Correlations). Some of the individuals reported with "isolated" eye findings were not sufficiently evaluated for features of *MYRF*-CUGS. Additionally, some of these individuals have related family members with the same pathogenic *MYRF* variant who have other system manifestations consistent with the *MYRF*-CUGS spectrum. For example, in one large kindred in which nanophthalmos segregated with a pathogenic splice site variant in *MYRF*, several of the affected individuals had dextrocardia and one had pulmonary hypoplasia [Garnai et al 2019]. In another family of five affected individuals, the proband had nanophthalmos only and the father had nanophthalmos and unilateral cryptorchidism; the other three individuals had more classic *MYRF*-CUGS findings [Gupta et al 2022].

Mild encephalitis / encephalopathy with reversible myelin vacuolization. This phenotype was described by Kurahashi et al [2018] in nine individuals from two unrelated families and was attributed to a specific *MYRF* pathogenic variant, c.1208A>G (p.Gln403Arg). It is unclear if this phenotype is distinct from *MYRF*-CUGS or is at one end of the phenotypic spectrum; thus far, there has been no reported overlap.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *MYRF*-Related Cardiac Urogenital Syndrome

Gene(s)	Disorder	MOI	Key Features	Distinguishing Features / Comment
FAM111A	Kenny-Caffey syndrome type 2 (KCS2) (See *FAM111A*-Related Skeletal Dysplasias.)	AD	Nanophthalmos, short stature, hypocalcemia, thickening medullary & cortical bone	KCS2 is assoc w/macrocephaly & low birth weight. [1]
GATA4	Testicular anomalies ± congenital heart disease (TACHD) (OMIM 615542)	AD	CHD, GU anomalies incl ambiguous genitalia	CDH, ocular, & pulmonary anomalies are not reported in TACHD. [2]
MFRP	MFRP-related nanophthalmos (OMIM 609549)	AR	Nanophthalmos, retinal degeneration	Syndromic features are not reported in *MFRP*-related nanophthalmos. [3]

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Key Features	Distinguishing Features / Comment
NR2F2	46,XX sex reversal (SRXX5) (OMIM 618901)	AD	46,XX ambiguous genitalia or sex reversal, müllerian anomalies, HLHS, CDH (1 person)	SRXX5 is assoc w/ambiguous (nonbinary) genitalia in 46,XX persons (vs 46,XY persons in CUGS) & eyelid anomalies; hyperopia is not reported. [4]
PIGL	*PIGL*-related disorder [5]	AR	CDH, ambiguous genitalia (1 family)	*PIGL*-related disorder is assoc w/ coloboma, vermian hypoplasia, & cleft palate. [5]
PRSS56	*PRSS56*-related nanophthalmos [6]	AR	Nanophthalmos, posterior microphthalmos	Syndromic features are not reported in *PRDD56*-related nanophthalmos. [6]
RLIM	Tonne-Kalscheuer syndrome (TOKAS) (OMIM 300978)	XL	DD, microcephaly, CHD, CDH, GU anomalies (cryptorchidism, hypospadias, micropenis)	TOKAS is assoc w/hypertelorism, a long, narrow face, & micrognathia. [7]
SPECC1L	Teebi hypertelorism syndrome 1 (TBHS1) (OMIM 145420)	AD	Hypertelorism, CDH, CHD, müllerian anomalies	In TBHS1, CDH is rare, pulmonary hypoplasia is only reported as secondary to CDH or omphalocele, hypertelorism is a prominent feature, & CHD are limited to ASD/VSD. [8]
TMEM98	*TMEM98*-related nanophthalmos (OMIM 615972)	AD	Nanophthalmos	Syndromic features have not been reported in *TMEM98*-related nanophthalmos. [9]
WT1	Meacham syndrome (See *WT1* Disorder.)	AD	CDH, pulmonary dysplasia, complex CHD, & GU abnormalities incl ambiguous genitalia & gonadal dysgenesis	A person w/clinical diagnosis of Meacham syndrome was later found to have *MYRF*-CUGS. [10]

AD = autosomal dominant; AR = autosomal recessive; ASD = atrial septal defect; CDH = congenital diaphragmatic hernia; CHD = congenital heart defects; GU = genitourinary; HLHS = hypoplastic left heart syndrome; *MYRF*-CUGS = *MYRF*-related cardiac urogenital syndrome; MOI = mode of inheritance; VSD = ventricular septal defect; XL = X-linked

1. Unger et al [2013]
2. Çelik et al [2022]
3. Zenteno et al [2009]
4. Bashamboo et al [2018]
5. Winter-Paquette et al [2022]
6. Nair et al [2011]
7. Mehvari et al [2020]
8. Zhang et al [2020]
9. Awadalla et al [2014]
10. Tanaka et al [2021]

Fryns syndrome is characterized by diaphragmatic defects, pulmonary hypoplasia, characteristic facial features, and short distal phalanges. Associated anomalies can include 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. Genetic heterogeneity for Fryns syndrome is likely. Biallelic pathogenic variants in *PIGN* have been identified in at least ten individuals with Fryns syndrome [Brady et al 2014, McInerney-Leo et al 2016, Alessandri et al 2018].

PAGOD syndrome (OMIM 202660). PAGOD (*p*ulmonary hypoplasia, *a*gonadism, *o*mphalocele, and *d*iaphragmatic hernia) syndrome and *MYRF*-related cardiac urogenital syndrome have significant clinical overlap [Rossetti et al 2019]. Hypoplastic left heart syndrome has been reported in several individuals with PAGOD. Significant undervirilization in 46,XY individuals or ambiguous genitalia is common [Gavrilova et al 2009]. The molecular basis of PAGOD is unknown at this time.

Management

No clinical practice guidelines for *MYRF*-related cardiac urogenital syndrome (*MYRF*-CUGS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MYRF*-CUGS, 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 *MYRF*-Related Cardiac Urogenital Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To identify short stature & microcephaly
Genitourinary	Thorough physical exam for phallic length, opening of urethral meatus, & location of gonads in 46,XY persons	If gonads are not palpable, pelvic & abdominal ultrasound may be considered.
	Consider pelvic ultrasound.	In 46,XX & 46,XY neonates & pubertal/postpubertal females [1]
	Renal ultrasound	Assess for structure & hydronephrosis.
Endocrine	Hormonal eval as directed by endocrinologist	For those w/46,XY DSD
	Consider TSH & free T4.	To evaluate for hypothyroidism in those w/poor growth &/or DD
Eyes	Ophthalmic eval	To assess for eye anomalies & refractive error
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Cardiovascular	Echocardiogram	To assess for congenital heart defects
Respiratory	Clinical assessment of breathing status & auscultation	Incl assessment of work of breathing & oxygen saturation, if clinically indicated
	Chest radiograph	To assess for pulmonary hypoplasia & diaphragmatic hernia
Gastrointestinal/ Feeding [2]	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status, esp in those w/cardiac &/or pulmonary malformations, delayed milestones, or neurologic deficits • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
	Consider upper GI exam w/small bowel follow through.	• To evaluate for malrotation • This is esp important when a PEG or gastrostomy tube is being considered.
	Consider abdominal ultrasound.	To evaluate for splenic anomalies & renal anomalies
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of *MYRF*-CUGS to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

DD = developmental delay; DSD = differences of sex development; PEG = percutaneous gastrostomy; MOI = mode of inheritance; *MYRF*-CUGS = *MYRF*-related cardiac urogenital syndrome; TSH = thyroid-stimulating hormone

1. Müllerian structures may be difficult to visualize on imaging in individuals who are not exposed to estrogen. Therefore, inability to visualize internal müllerian structures on imaging does not rule out their presence. Examination under anesthesia and/or laparoscopy may be required to detect the presence of müllerian structures and to define any müllerian anomalies.

2. Growth and feeding issues are often secondary complications in affected individuals with cardiopulmonary issues.

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

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in cardiology, endocrinology, genetics, gastroenterology, gynecology, ophthalmology, pulmonology, psychology, and urology (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *MYRF*-Related Cardiac Urogenital Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Undervirilization or ambiguous (nonbinary) genitalia in 46,XY persons	Standard therapy per DSD team [1]	Which may incl hormonal therapy, psychosocial support, gender identity assessment, & surgical intervention (e.g., orchidopexy &/or hypospadias repair)
Low or absent serum testosterone levels [2]	• After age 14 yrs, low-dose testosterone replacement therapy can be initiated [3, 4]: testosterone enanthate [5] is given IM [6] every 3-4 wks starting at 100 mg & ↑ by 50 mg every 6 mos to 200-400 mg. • In adulthood, the treatment should plateau, at best possible dosage, typically between 50 & 400 mg every 2-4 wks.	• If person has short stature & is eligible for growth hormone therapy, either delay testosterone therapy or give at lower doses initially to maximize growth potential. • Side effects incl pain assoc w/ injection & large variations of serum testosterone concentration between injections, resulting in ↑ risk of mood swings.
Ovarian hypoplasia	Referral to gynecologist or reproductive endocrinologist for discussion of initiating/ continuing HRT & fertility options	
Hypothyroidism	Thyroid replacement therapy	Per endocrinologist
Refractive error, amblyopia, angle closure glaucoma, nanophthalmos	Standard treatment per ophthalmologist	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Structural cardiac abnormalities	Standard treatment per cardiologist	
Diaphragmatic hernia	Standard treatment per surgeon & pulmonologist	
Pulmonary hypoplasia	Standard treatment per pulmonologist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Intestinal malrotation	Standard treatment per surgeon & gastroenterologist	
Splenic anomalies	Standard treatment per immunologist	
Renal anomalies / Hydronephrosis	Standard treatment per urologist &/or nephrologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for learning or developmental supports

DSD = differences of sex development; HRT = hormone replacement therapy; IM = intramuscular
1. The DSD team should include geneticist, endocrinologist, psychologist, urologist, and possibly gynecologist. If a multidisciplinary team is unavailable, these specialties can be consulted individually.
2. Prior to initiating treatment with supplemental testosterone in adults, perform a digital rectal examination and measurement of prostate-specific antigen, abnormalities of which would be a contraindication to the treatment.
3. Physicians should check for the most current preparations and dosage recommendations before initiating testosterone replacement therapy.
4. Initial high doses of testosterone should be avoided to prevent priapism.
5. Injection of testosterone enanthate is the preferred method of replacement therapy because of low cost and easy, at-home regulation of dosage.
6. Alternative delivery systems that result in a more stable dosing include transdermal patches (scrotal and nonscrotal) and transdermal gels. Testosterone-containing gels, however, are associated with the risk of interpersonal transfer, which can be reduced by the use of newer hydroalcoholic gels.

Developmental Delay / Intellectual Disability 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 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).

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

Communication. Speech-language therapy is recommended for those with speech delay.

Surveillance

Table 6. Recommended Surveillance for Individuals with *MYRF*-Related Cardiac Urogenital Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters	At each visit
Endocrine	Monitor for onset & progression of puberty.	At each visit starting at age ~7 yrs until puberty is completed
Low testosterone levels	Assessment of mood, libido, energy, erectile function, acne, breast tenderness, & presence or progression of gynecomastia	At each visit in undervirilized 46,XY adolescents & adults
For those on testosterone replacement therapy	Measurement of serum testosterone levels	At 3-mo intervals (prior to next injection) to evaluate nadir testosterone concentrations [1]; once optimal dose is established, annual measurement is sufficient.
	Digital rectal exam & measurement of PSA in adults [2]	3, 6, & 12 mos after initiation of testosterone therapy; then annually
	Measurement of hematocrit [3]	
	Lipid profile & liver function tests	Annually
Eyes	Ophthalmic eval	Annuall, or as clinically indicated if features of amblyopia, strabismus, or angle closure glaucoma are present

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Respiratory	Monitor for evidence of respiratory insufficiency.	
Osteopenia	DXA scan in persons w/DSD	Every 3-5 yrs after puberty, or annually if osteopenia has been identified
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

DXA = dual-energy x-ray absorptiometry; DSD = differences of sex development; PSA = prostate-specific antigen
1. Concentrations lower than 200 ng/dL or higher than 500 ng/dL may require adjustment of total dose or frequency.
2. To evaluate for the presence of an overt prostate cancer, which would be a contraindication to supplemental testosterone treatment
3. Increased hematocrit may lead to a subsequent risk of hypoxia and sleep apnea.

Agents/Circumstances to Avoid

Contraindications to hormone replacement therapy include hormone-responsive cancers.

Oral androgens such as methyltestosterone and fluoxymesterone should not be given in hormone replacement therapy (especially for long-term therapy) because of liver toxicity.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of screening and treatment measures. Intrafamilial variability of affected individuals is high, and features may be previously underappreciated in a family.

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

MYRF-related cardiac urogenital syndrome (*MYRF*-CUGS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals with *MYRF*-CUGS reported to date have the disorder as the result of a *de novo MYRF* pathogenic variant.
- In some families, individuals with *MYRF*-CUGS have the disorder as the result of a pathogenic variant inherited from a heterozygous parent [Gupta et al 2022]. Of note, the presentation of *MYRF*-CUGS can be extremely variable within families and a heterozygous parent may be asymptomatic or very mildly affected.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status, determine their need for screening and treatment (see Management), 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 in the germ cells only.

      * A parent with somatic and germline mosaicism for a *MYRF* pathogenic variant may be asymptomatic or mildly/minimally affected [Garnai et al 2019].

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The manifestations of *MYRF*-CUGS within a family are highly variable and sibs who inherit a *MYRF* pathogenic variant may have significantly more or fewer manifestations than the proband. Molecular genetic testing is recommended for the sibs of the proband to determine their need for screening and treatment (see Management).
- If the *MYRF* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism [Garnai et al 2019].
- If the parents have not been tested for the *MYRF* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *MYRF*-CUGS because of the possibility of variable expressivity in a heterozygous parent or parental germline mosaicism.

Offspring of a proband

- Each child of an individual with *MYRF*-CUGS has a 50% chance of inheriting the *MYRF* pathogenic variant.
- Manifestations within a family are highly variable and offspring may have significantly more or fewer manifestations than the proband.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *MYRF* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MYRF* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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.

- **Accord Alliance**
  Phone: 602-492-4144
  www.AccordAlliance.org
- **CDH International**
  Email: info@cdhi.org
  cdhi.org
- **DSD Families**
  United Kingdom
  Email: info@dsdfamilies.org
  www.dsdfamilies.org/charity
- **InterConnect**
  https://interconnect.support/
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **The Children's Heart Foundation**
  Phone: 847-634-6474
  Email: info@childrensheartfoundation.org
  www.childrensheartfoundation.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. MYRF-Related Cardiac Urogenital Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
MYRF	11q12.2	Myelin regulatory factor	MYRF	MYRF

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 MYRF-Related Cardiac Urogenital Syndrome (View All in OMIM)

608329	MYELIN REGULATORY FACTOR; MYRF
618280	CARDIAC-UROGENITAL SYNDROME; CUGS

Molecular Pathogenesis

MYRF encodes myelin regulatory factor, a membrane-bound transcription factor which is proteolytically cleaved into its C- and N-terminal domains. The C-terminal fragment remains in the endoplasmic reticulum while the N-terminal region, which contains the DNA-binding domain, travels to the nucleus, where it promotes the expression of target genes. *MYRF* has been shown to be expressed in a wide range of tissues including the heart, lung, diaphragm, eye, and coelomic epithelium of the fetal gonads. The coelomic epithelium of fetal gonads forms the germinal epithelium, which may account for the differences of sex development phenotype seen in some individuals with pathogenic variants in *MYRF*. It has therefore been postulated that *MYRF* may be involved in the development of coelomic epithelium-derived cells and tissues.

Mechanism of disease causation. Loss of function

Table 7. Notable *MYRF* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_001127392.3	c.3376-1G>A	--	Pathogenic variant assoc w/nanophthalmos [Garnai et al 2019]

Chapter Notes

Author Notes

Louisa (Louise) C Pyle, MD, PhD is a clinical geneticist and physician-scientist specializing in genetics of genitourinary (GU) differences and cancer. Dr Pyle's clinical interests are diagnostic evaluation and care for individuals with intersex (I) traits and differences of sex development (DSD), and other GU differences. She focuses on multidisciplinary integration, molecular diagnosis, and cancer predisposition counseling for her patients and their families. Dr Pyle's research applies genomics and human models to understand vulnerability to infertility and germ cell tumor (GCT). She has identified and characterized clinical risk factors that predispose people to GCT by studying individuals diagnosed with this malignancy, as well as patients carrying a diagnosis of I/DSD. Dr Pyle's goal is to supply new tools that will facilitate improved care for people with I/DSD traits. Web page: childrensnational.org/visit/find-a-provider/louise-pyle

Lev Prasov, MD, PhD, is a physician-scientist practicing ophthalmic genetics. His clinical interests are in the diagnostic evaluation and treatment of inherited ocular disorders with specific interests in disorders of refractive error, glaucoma, ocular malformations and inherited retinal diseases. Dr Prasov's research seeks to identify novel

genes and pathways in inherited ocular conditions with the hope of developing or improving therapies for these conditions. He uses a combination of human genetics and mammalian and cell culture models to identify and validate disease genes and to identify novel pathways for pathogenesis. Web page: prasov.lab.medicine.umich.edu/about

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