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MIRAGE Syndrome

Synonym: Myelodysplasia, Infection, Restriction of Growth, Adrenal Hypoplasia, Genital Phenotypes, and Enteropathy

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Summary

Clinical characteristics

MIRAGE syndrome is an acronym for the major findings of *m*yelodysplasia, *i*nfection, *r*estriction of growth, *a*drenal hypoplasia, *g*enital phenotypes, and *e*nteropathy. Cytopenias are typically seen soon after birth; thrombocytopenia is the most common followed by anemia and pancytopenia. Recurrent infections from early infancy include pneumonia, urinary tract infection, gastroenteritis, meningitis, otitis media, dermatitis, subcutaneous abscess, and sepsis. Reported genital phenotypes in those with 46,XY karyotype included hypospadias, microphallus, bifid shawl scrotum, ambiguous genitalia, or complete female genitalia. Hypoplastic or dysgenetic ovaries have been reported in females. Gastrointestinal complications include chronic diarrhea and esophageal dysfunction. Moderate-to-severe developmental delay is reported in most affected individuals. Autonomic dysfunction and renal dysfunction are also reported.

Diagnosis/testing

The diagnosis of MIRAGE syndrome is established in a proband with suggestive findings and a heterozygous germline gain-of-function pathogenic variant in *SAMD9* identified by molecular genetic testing.

Management

Treatment of manifestations: Individuals with severe anemia and thrombocytopenia due to bone marrow failure should be treated with standard transfusion approaches; bacterial infection prevention including antibiotic prophylaxis and fever precautions in individuals with severe neutropenia. Individuals with severe neutropenia and chronic transfusion requirements, along with individuals who develop monosomy 7 myelodysplastic syndrome should be considered for hematopoietic stem cell transplantation. Standard treatment of infections

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with antibiotics, antiviral or antifungal agents as needed; consider prophylactic intravenous immunoglobulin if endogenous immunoglobulin levels are low; management by nutritionist to ensure adequate caloric intake and to assist with elemental diet for chronic diarrhea; hydrocortisone and fludrocortisone as needed for adrenal hypoplasia; surgical removal of dysgenetic gonads or surgical intervention may be considered for those with external genital anomalies; consider duodenal tube feeding in those with recurrent aspiration pneumonia; early intervention with occupational, physical, speech and feeding therapy for developmental delay; artificial tear solutions and treatment per ophthalmologist for ocular manifestations of autonomic dysfunction such as hypolacrima; management of ambient temperature for those with temperature instability; management of renal dysfunction per nephrologist.

Surveillance: Complete blood count with differential every four to six months; annual bone marrow aspirate and biopsy (with analysis for somatic alterations including chromosome 7 abnormalities) in those with cytopenias including anemia, thrombocytopenia, or neutropenia; at least annual assessment of height, weight, head circumference, physical examination for features of adrenal hypoplasia, and measurement of serum sodium, potassium, glucose, cortisol, and ACTH. Assess for diarrhea, feeding issues, and esophageal dysfunction as needed; monitor developmental milestones every three to six months in the first year of life and at least annually thereafter; assess for keratoconjunctivitis sicca, corneal ulcer, and temperature instability as needed; at least annual measurement of serum creatinine, blood urea nitrogen, and urinalysis to evaluate renal function.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from evaluation for myelodysplasia.

Genetic counseling

MIRAGE syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, individuals diagnosed with MIRAGE syndrome have the disorder as the result of a variant inherited from a heterozygous parent with no apparent features of MIRAGE syndrome. If the proband has an *SAMD9* pathogenic variant that is not 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 germline mosaicism or the possibility of a false negative result in a parent due to preferential loss of the chromosome with the *SAMD9* pathogenic variant. Once the *SAMD9* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for MIRAGE syndrome have not been established.

Suggestive Findings

MIRAGE syndrome **should be suspected** in individuals with the following clinical, laboratory, and radiographic features.

Clinical features

- Easy bruising, mucocutaneous bleeding, oral ulcers, fatigue, pallor
- Recurrent bacterial infections including pneumonia, urinary tract infection, gastroenteritis, meningitis, otitis media, dermatitis, subcutaneous abscess, and sepsis. The most common organisms associated with these infections are enteric pathogens such as *Klebsiella* and *Enterococcus*. Affected individuals may also be at higher risk for viral (e.g., cytomegalovirus), bacterial respiratory pathogens, and fungal infections (e.g., *Candida*).
- Growth deficiency (intrauterine growth restriction with premature birth; persistent failure to thrive)

- Diffuse skin hyperpigmentation, severe dehydration, and hypotension (due to primary adrenal insufficiency) which may be life threatening
- Atypical external genitalia in 46,XY individuals (e.g., hypospadias, microphallus, bifid shawl scrotum, ambiguous genitalia, or complete female genitalia)
- Chronic intractable diarrhea
- Dysphagia, recurrent aspiration pneumonia, gastroesophageal reflux

Laboratory features

- Mono- or multilineage cytopenia, either transient or persistent
- Bone marrow aspirate and biopsy may show hypocellularity/aplasia with absent megakaryocytes, or it may show myelodysplastic syndrome and/or acute myelogenous leukemia (AML) with monosomy 7. Monosomy 7 may be transient if the clone is small, or it may persist for years before transformation to AML. Additional somatic pathogenic variants may correlate with transformation to AML.
- Laboratory features of primary adrenal insufficiency: hyponatremia, hyperkalemia, hypoglycemia, low cortisol, and markedly elevated corticotropin (ACTH). Impaired cortisol response to cosyntropin stimulation is a confirmatory finding of primary adrenal insufficiency.

Radiographic features

- Adrenal aplasia or hypoplasia on ultrasound
- Microcephaly, hydrocephalus, and white matter abnormalities on brain MRI

Establishing the Diagnosis

The diagnosis of MIRAGE syndrome **is established** in a proband with suggestive findings and a heterozygous germline gain-of-function pathogenic variant in *SAMD9* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *SAMD9* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

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 with a phenotype indistinguishable from many other inherited disorders with growth restriction, myelodysplasia, and/or adrenal hypoplasia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SAMD9* is performed first to detect a heterozygous germline gain-of-function pathogenic variant. If feasible, use of DNA derived from non-hematopoietic tissue (e.g., skin fibroblasts, hair roots) may be considered, as germline pathogenic variants may not be detectable in leukocytes in some individuals (see Molecular Genetics, ***SAMD9*-specific laboratory technical considerations**).

Note: (1) A germline *SAMD9* pathogenic variant may not be identified in an individual with somatically acquired loss of heterozygosity, which often occurs in hematopoietic tissue of individuals with a germline gain-of-function *SAMD9* pathogenic variant (see Table 1, footnote 5). (2) Sequence analysis of *SAMD9* in hematopoietic tissue may identify a secondary (postzygotic) loss-of-function *SAMD9* variant *in cis* with the germline gain-of-function *SAMD9* pathogenic variant associated with MIRAGE syndrome [Roucher-Boulez et al 2019].

An adrenal hypoplasia or myelodysplasia multigene panel that includes *SAMD9* and other genes of interest (see Differential Diagnosis) may be considered 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*. Of note, given the rarity of MIRAGE syndrome, some panels may not include *SAMD9*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by growth restriction, myelodysplasia, and/or adrenal hypoplasia, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is the best 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 MIRAGE Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SAMD9	Sequence analysis [3]	44/44 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Somatically acquired loss of heterozygosity – for example, due to monosomy 7, del(7q), or uniparental disomy 7 – often occurs in hematopoietic tissue of individuals with a pathogenic *SAMD9* variant. *SAMD9* is located on chromosome 7 and loss of chromosomes with a pathogenic *SAMD9* variant occurs preferentially. This somatic change results in a decreased fraction of cells with the variant and may cause a false negative molecular result when testing leukocyte or bone marrow DNA. Therefore, evaluation of genomic abnormalities with SNP array and/or evaluation of low-abundance variants with deep sequencing (>1000X read depth) should be considered in individuals who are clinically suspected for MIRAGE syndrome and have a negative genetic test result. If feasible, use of DNA derived from non-hematopoietic tissues (e.g. skin fibroblasts, hair roots) may be considered (see Molecular Genetics, ***SAMD9*-specific laboratory technical considerations**).
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available. In theory, deletion of *SAMD9* would cause loss of function and therefore would not cause MIRAGE syndrome.

Clinical Characteristics

Clinical Description

MIRAGE syndrome is a rare disorder characterized by six core features: *m*yelodysplasia, *i*nfection, *r*estriction of growth, *a*drenal hypoplasia, *g*enital phenotypes, and *e*nteropathy.

To date, no consensus clinical diagnostic criteria for MIRAGE syndrome are available. In this review, a diagnosis of MIRAGE syndrome is defined as:

- 46,XY individuals with four or more of the core features; or
- 46,XX individuals with three or more of the core features.

Using these diagnostic criteria, 44 individuals with features of MIRAGE syndrome and a pathogenic variant in *SAMD9* have been identified to date [Narumi et al 2016, Buonocore et al 2017, Bluteau et al 2018, Jeffries et al 2018, Kim et al 2018, Sarthy et al 2018, Shima et al 2018a, Shima et al 2018b, Wilson et al 2018, Ahmed et al 2019, Csillag et al 2019, Formankova et al 2019, Mengen et al 2020, Perisa et al 2019, Roucher-Boulez et al 2019, Yoshizaki et al 2019, Zhang et al 2019, Onuma et al 2020, Viaene & Harding 2020]. The following description of the phenotypic features associated with MIRAGE syndrome is based on these reports.

Table 2. MIRAGE Syndrome: Frequency of Select Features

Feature	# of Persons w/Feature	Comment
Myelodysplasia	37/44	Some assoc w/monosomy 7 or del(7q)
Recurrent infection	40/44	
Restriction of growth	43/44	
Adrenal hypoplasia	34/44	
Atypical external genitalia in 46,XY individuals	33/34	Hypospadias, microphallus, bifid shawl scrotum, ambiguous genitalia, or complete female genitalia
Gastrointestinal complications	36/44	

Myelodysplasia and bone marrow failure. Age of onset of hematologic abnormalities is variable. Two distinct groups with respect to prognosis and severity of cytopenias include individuals diagnosed with severe cytopenias between birth and age two years (~60%) and individuals diagnosed later in childhood (~40%) [Rentas et al 2020]. Prior to the onset of hematopoietic clonal evolution, individuals may present with bone marrow hypoplasia and features consistent with congenital amegakaryocytic thrombocytopenia [Sarthy et al 2018]. Thrombocytopenia is the most common manifestation, followed by anemia and pancytopenia. Severe cytopenias may occur in distinct acute episodes associated with myelosuppressive infections or may be chronic, requiring frequent transfusions. Of note, cytopenias may improve with age in some individuals.

Evolution to myelodysplastic syndrome (MDS) is defined by acquisition of monosomy 7 or del(7q) in the setting of multilineage bone marrow dysplasia. Although myelodysplasia is included as a core feature of MIRAGE syndrome, myelodysplasia in these individuals appears to be due to an acquired deletion of *SAMD9*, primarily of the *SAMD9* allele with a germline gain-of-function pathogenic variant. Notably, individuals with a germline gain-of-function *SAMD9* pathogenic variant may acquire somatic alterations (including uniparental disomy 7 or *SAMD9* pathogenic variants *in cis* with the germline variant) that do not predispose to MDS and may actually improve hematopoietic function (see Penetrance).

Individuals with a germline gain-of-function *SAMD9* pathogenic variant may present with myelodysplasia and develop no additional or only limited features of MIRAGE syndrome [Schwartz et al 2017, Hockings et al 2020].

Recurrent infections. Most individuals with MIRAGE syndrome develop recurrent bacterial infections from early infancy including pneumonia, urinary tract infection, gastroenteritis, meningitis, otitis media, dermatitis, subcutaneous abscess, and sepsis. The most common organisms associated with these infections are enteric pathogens such as *Klebsiella* and *Enterococcus*. Affected individuals may also be at higher risk for complications from both viral (e.g., cytomegalovirus) and bacterial respiratory pathogens. Affected individuals with severe immune deficiency due either to native immune dysfunction or to stem cell transplant are also at risk for severe fungal infections (e.g., *Candida*). To date, the etiology of the increased susceptibility to infections is unknown. It may be partly explained by hypogammaglobulinemia or lymphopenia. In four individuals, the thymus was hypoplastic [Narumi et al 2016, Sarthy et al 2018]. Incomplete lasting immunity to vaccinations has been reported in two affected individuals [Jeffries et al 2018].

Growth restriction / growth deficiency. Typically, affected individuals are delivered premature by emergency cæsarean section due to fetal growth failure and suspected fetal distress. Most individuals have persistent growth deficiency (weight, height/length, and head circumference are commonly all below -2.0 SD) despite adequate caloric supply, with the exception of two individuals who showed normal growth after birth [Shima et al 2018b, Roucher-Boulez et al 2019].

Adrenal hypoplasia. Approximately 80% of individuals have primary adrenal insufficiency. They present with prominent diffuse skin hyperpigmentation at birth and may develop severe dehydration and hypotension, which can be life-threatening. The diagnosis of primary adrenal insufficiency is confirmed by low cortisol and markedly elevated ACTH levels. Aplastic or hypoplastic adrenal glands are found on ultrasound examination. Rarely, adrenal insufficiency may emerge in late childhood [Perisa et al 2019].

Genital anomalies. Reported findings in those with 46,XY karyotype included hypospadias, microphallus, bifid shawl scrotum, ambiguous genitalia, or complete female genitalia. The testes were usually hypoplastic or dysgenetic. One individual, age three days, was reported to have undetectable testosterone [Roucher-Boulez et al 2019]. One individual, age 16 years, was reported to have testicular failure [Wilson et al 2018].

No external genital anomalies were reported in individuals with 46,XX karyotype, but four were found to have hypoplastic or dysgenetic ovaries [Narumi et al 2016, Sarthy et al 2018, Viaene & Harding 2020].

Gastrointestinal complications. Chronic diarrhea occurs in about 80% of affected individuals and often results in severe diaper rash. It usually occurs after initiating enteral nutrition. About one third of individuals with MIRAGE syndrome have esophageal problems often accompanied by recurrent aspiration pneumonia. Clinical manifestations include dysphagia, gastroesophageal reflux, vomiting, esophageal hypoperistalsis, esophageal stricture, and achalasia.

Neurologic development. Moderate-to-severe developmental delay is reported in most affected individuals. Reported individuals are often nonambulatory with absent or limited language development. Neuropathologic findings such as microcephaly, hydrocephalus, white matter abnormalities, and perivascular calcifications may be present [Viaene & Harding 2020].

Autonomic dysfunction. Symptoms compatible with autonomic dysfunction such as hypolacrima with corneal ulcer, hypo/anhidrosis with temperature instability, or hyperhidrosis were reported in seven individuals [Jeffries et al 2018, Sarthy et al 2018, Shima et al 2018a, Shima et al 2018b].

Renal dysfunction including proteinuria and renal tubular acidosis were reported in five of 17 individuals who lived beyond age three years. Renal biopsies were performed in four individuals; two were found to have focal segmental glomerular sclerosis [Ahmed et al 2019, Perisa et al 2019], one to have interstitial nephritis [Shima et al 2018b], and one to have C1q nephropathy [Wilson et al 2018].

Prognosis. The median age of death in affected individuals is three years. Nearly 60% of the deaths were due to infectious diseases. The oldest affected individual was reported to be alive at age 20 years [Bluteau et al 2018].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance is unknown. Of note, one asymptomatic female with a germline gain-of-function *SAMD9* pathogenic variant (which she transmitted to her child, who had a typical MIRAGE phenotype) also had a somatic loss-of-function *SAMD9* variant *in cis*, presumably acquired in an early stage of development [Roucher-Boulez et al 2019].

Prevalence

To date, 44 affected individuals have been reported.

Genetically Related (Allelic) Disorders

Normophosphatemic familial tumoral calcinosis. Biallelic loss-of-function *SAMD9* pathogenic variants p.Lys1495Glu and p.Arg344Ter are associated with normophosphatemic familial tumoral calcinosis (OMIM 610455). There is no phenotypic overlap between normophosphatemic familial tumoral calcinosis and MIRAGE syndrome.

Germline *SAMD9* loss of function in adult myelodysplastic syndrome (MDS). Germline loss-of-function *SAMD9* variants leading to increased cell proliferation capacity may be associated with adult MDS [Nagata et al 2018].

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of MIRAGE Syndrome

Gene	DiffDx Disorder	MOI	Features of MIRAGE Syndrome	
			Also observed in DiffDx disorder	Not observed in DiffDx disorder
AAAS	Triple A syndrome (OMIM 231550)	AR	Primary adrenal insufficiency, achalasia, alacrima	Hematologic abnormalities, recurrent infections, growth restriction, genital problems, diarrhea
CDKN1C	IMAGe syndrome	AD [1]	IUGR, adrenal hypoplasia, genital anomalies	Hematologic abnormalities, recurrent infections, diarrhea
GATA2	GATA2 deficiency [2, 3]	AD	Cytopenias, MDS w/monosomy 7, immunodeficiency, infections, genital anomalies	Adrenal hypoplasia, growth restriction, diarrhea
POLE	IMAGe-I (OMIM 618336)	AR	IUGR, adrenal hypoplasia, genital anomalies, immunodeficiency	Hematologic abnormalities, diarrhea

Table 3. continued from previous page.

Gene	DiffDx Disorder	MOI	Features of MIRAGE Syndrome	
			Also observed in DiffDx disorder	Not observed in DiffDx disorder
SAMD9L	*SAMD9L* ataxia-pancytopenia syndrome [3]	AD	Cytopenias, MDS w/monosomy 7, immunodeficiency, infections	Adrenal hypoplasia, growth restriction, diarrhea, genital anomalies

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; IMAGe-I = *i*ntrauterine growth restriction, *m*etaphyseal dysplasia, *a*drenal hypoplasia congenita, *ge*nital anomalies, and *i*mmunodeficiency; IUGR = intrauterine growth restriction; MDS = myelodysplastic syndrome; MOI = mode of inheritance

1. A *CDKN1C* pathogenic variant causing IMAGe syndrome is typically inherited in an autosomal dominant manner; however, only maternal transmission of the pathogenic variant results in IMAGe syndrome.

2. Wlodarski et al [2016]

3. See also Monosomy 7 Predisposition Syndromes Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MIRAGE 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 MIRAGE Syndrome

System/Concern	Evaluation	Comment
Myelodysplasia & bone marrow failure	• Referral to hematologist • CBC w/differential • Bone marrow aspirate & biopsy	Those w/severe cytopenia or monosomy 7 MDS may need referral for stem cell transplantation. [1]
Recurrent infections	• Obtain history of infections incl pathogens. • Eval of lymphocyte subsets & IgG levels • Assess for vaccine responses.	To assess susceptibility for infectious diseases
Growth deficiency	Assessment of length/height, weight, & head circumference using standard growth charts	
Adrenal hypoplasia	Endocrinologic eval incl measurement of serum sodium, potassium, glucose, & cortisol; plasma ACTH. Consider adrenal ultrasound.	• To assess for primary adrenal insufficiency • Consider consultation w/endocrinologist.
Genital anomalies	Clinical exam of external genitalia	Consider referral to endocrinologist.
	Chromosome analysis	Required even if external genitalia appear phenotypic female
Gastrointestinal complications	Gastroenterology / nutrition / feeding team eval to assess for diarrhea, feeding issues, esophageal dysfunction	• To incl eval of aspiration risk & nutritional status • Consider eval for duodenal tube placement in those w/dysphagia &/or aspiration risk.
Developmental delay	Developmental eval	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Autonomic dysfunction	Autonomic nervous system eval incl assessment for hypolacrima, keratoconjunctivitis sicca, corneal ulcer, dyshidrosis, & temperature instability	Consider referral to a neurologist &/or ophthalmologist.
Renal dysfunction	• Serum creatinine & blood urea nitrogen • Urinalysis	To assess for proteinuria & evidence of renal tubular acidosis

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [2]	To inform patients & their families re nature, MOI, & implications of MIRAGE syndrome in order to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

CBC = complete blood count; MDS = myelodysplastic syndrome; MOI = mode of inheritance
1. See Monosomy 7 Predisposition Syndromes Overview, Management.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with MIRAGE Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Myelodysplasia & bone marrow failure	• Transfusion support for severe anemia & thrombocytopenia • Bacterial infection prevention strategies incl antibiotic prophylaxis & fever precautions in those w/severe neutropenia • HSCT is curative treatment for myelodysplasia, chronic severe neutropenia, or chronic transfusion dependence. [1]	In persons w/severe & persistent cytopenia: eval for monosomy 7 [2]
Infection	• Treatment w/antibiotics, antivirals, & antifungals as needed • Prophylactic IV Ig if endogenous Ig levels are ↓	
Growth deficiency	Mgmt by nutritionist to ensure adequate caloric intake	
Adrenal hypoplasia	HRT w/hydrocortisone & fludrocortisone per endocrinologist	
Genital anomalies	Surgical removal of dysgenetic gonads or surgical intervention may be considered for those w/external genital anomalies.	Consult w/interdisciplinary care team (clinical geneticists, endocrinologists, surgeons, & mental health professionals) when assigning sex of rearing & deciding mgmt plan.
Diarrhea	Elemental diet	Rule out other treatable cause(s) of diarrhea.
Esophageal dysfunction	Consider duodenal tube feeding in those w/recurrent aspiration pneumonia. [3]	
Developmental delay	Referral to an early intervention program for occupational, physical, speech, & feeding therapy	Consultation w/developmental pediatrician to ensure involvement of appropriate community, state, & educational agencies & to support parents in maximizing quality of life
Autonomic dysfunction	• Use of artificial tear solutions & treatment per ophthalmologist • Mgmt of ambient temperature for those w/temperature instability	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Renal dysfunction	Treatment per nephrologist	

HRT = hormone replacement therapy; HSCT = hematopoietic stem cell transplantation; Ig = immunoglobulin; IV = intravenous
1. Presence of adrenal hypoplasia may complicate transplantation, requiring extreme care.
2. Monosomy 7 greatly increases the risk for treatment-resistant leukemia.
3. Yoshizaki et al [2019]

Hematopoietic stem cell transplantation (HSCT). Two published reports detail the outcomes of 12 individuals undergoing HSCT to treat either MDS or bone marrow failure associated with germline *SAMD9* pathogenic variants [Sarthy et al 2018, Ahmed et al 2019]. Donors for these individuals include matched related, closely matched unrelated, and mismatch related (haploidentical) donors. Of the eight individuals with MIRAGE syndrome, all experienced severe complications including adrenal crisis with blood pressure instability and electrolyte imbalances, severe systemic infections, and organ dysfunction including hepatic venoocclusive disease and respiratory failure. Three of the eight individuals with severe MIRAGE syndrome manifestations died of these complications post transplant. Based on these results, while HSCT should be considered for individuals with severe hematologic disease associated with MIRAGE syndrome, physicians need to make individuals and families aware that HSCT may exacerbate preexisting organ dysfunction for individuals with MIRAGE syndrome and can lead to organ failure and death. Thus, in some instances non-curative supportive care for hematologic disease may be preferable to HSCT for optimization of quality of life.

Surveillance

No formal surveillance guidelines are available. The recommendations in Table 6 are based on the authors' personal experience.

Table 6. Recommended Surveillance for Individuals with MIRAGE Syndrome

System/Concern	Evaluation	Frequency
Myelodysplasia & bone marrow failure	Complete blood count w/differential	Every 4-6 mos
	Bone marrow aspirate & biopsy w/analysis for somatic alterations incl chromosome 7 abnormalities	Annually for all persons w/cytopenias
Growth	Assessment of length/height, weight, head circumference	At least annually
Adrenal hypoplasia	• Physical exam for features of adrenal hypoplasia • Serum sodium, potassium, glucose, cortisol, ACTH	
Gastrointestinal complications	Assess for diarrhea, feeding issues, esophageal dysfunction.	As needed
Developmental delay	Monitor developmental milestones.	Every 3-6 mos in 1st yr of life; at least annually thereafter
Autonomic dysfunction	Assess for keratoconjunctivitis sicca, corneal ulcer, dyshidrosis, temperature instability.	As needed
Renal dysfunction	Serum creatinine, blood urea nitrogen, urinalysis	At least annually

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 early evaluation for myelodysplasia. (See Molecular Genetics, ***SAMD9*-specific laboratory technical considerations**.)

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

MIRAGE syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with MIRAGE syndrome have the disorder as the result of a *de novo SAMD9* pathogenic variant.
- Rarely, individuals diagnosed with MIRAGE syndrome have the disorder as the result of an *SAMD9* pathogenic variant inherited from a heterozygous parent with no apparent features of MIRAGE syndrome [Roucher-Boulez et al 2019].
- Molecular genetic testing is recommended for the parents of the proband. If the pathogenic variant found in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental leukocyte DNA; and (2) parental identity testing has confirmed biological maternity and paternity; if parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline mosaicism. Presumed parental germline mosaicism has been reported for MIRAGE syndrome; however, parental identity testing was not performed in the reported family [Narumi et al 2016].
  - The proband inherited a pathogenic variant from a parent with somatically acquired loss of heterozygosity with preferential loss of the chromosome with a pathogenic *SAMD9* variant. This somatic change (e.g., due to monosomy 7 or uniparental disomy 7) often occurs in hematopoietic tissue of individuals with a pathogenic *SAMD9* variant and results in a decreased fraction of cells with the variant, and may cause a false negative molecular result when testing leukocyte DNA (see Molecular Genetics, ***SAMD9*-specific laboratory technical considerations**).
- Although rarely reported, the clinical family history of some individuals diagnosed with MIRAGE syndrome may appear to be negative because of failure to recognize the disorder in family members,

reduced penetrance, or phenotypic modification resulting from a natural protective second genetic event (see Penetrance). Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing (optimally using DNA derived from non-hematopoietic tissue) has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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 has the *SAMD9* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Sibs who inherit a pathogenic variant will likely manifest the MIRAGE syndrome phenotype (see Penetrance).
- If the proband has a known *SAMD9* pathogenic variant that 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 germline mosaicism and the possibility of a false negative result in a parent due to preferential loss of the chromosome with the *SAMD9* pathogenic variant [Narumi et al 2016].
- If the parents have not been tested for the *SAMD9* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for MIRAGE syndrome because of the possibility that either: (1) a parent has germline mosaicism; or (2) a parent is heterozygous but does not have apparent manifestations of MIRAGE syndrome because of reduced penetrance or phenotypic modification resulting from a natural protective second genetic event (see Penetrance).

Offspring of a proband

- Each child of an individual with a heterozygous *SAMD9* pathogenic variant has a 50% chance of inheriting the pathogenic variant.
- To date, individuals with the typical MIRAGE syndrome phenotype are not known to reproduce, likely owing to the severity of the condition and/or primary gonadal dysfunction.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SAMD9* pathogenic variant, his or her family members may be at risk of having an *SAMD9* pathogenic variant and associated clinical manifestations including myelodysplasia (see Clinical Description).

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 may be at risk of having a child with MIRAGE syndrome.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SAMD9* 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.

- **Genetic and Rare Diseases Information Center (GARD)**
  PO Box 8126
  Gaithersburg MD 20898-8126
  Phone: 888-205-2311 (toll-free); 888-205-3223 (toll-free TTY); 301-519-3194
  Fax: 301-251-4911
  Email: GARDinfo@nih.gov
  MIRAGE syndrome

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. MIRAGE Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
SAMD9	7q21	Sterile alpha motif domain-containing protein 9	SAMD9

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 MIRAGE Syndrome (View All in OMIM)

610456	STERILE ALPHA MOTIF DOMAIN-CONTAINING PROTEIN 9; SAMD9
617053	MIRAGE SYNDROME; MIRAGE

Molecular Pathogenesis

SAMD9, a single-exon gene, encodes SAMD9, which has a mild antiproliferative capacity. Abnormal SAMD9 protein with disease-associated variants has an exaggerated antiproliferative capacity. These observations suggest that MIRAGE syndrome is caused by dysregulated activation of SAMD9. The majority of MIRAGE syndrome-causing variants are private missense alterations, with 21 unique variants found in 29 individuals (summarized in Rentas et al [2020]).

Mechanism of disease causation. Gain of function

***SAMD9*-specific laboratory technical considerations.** Somatically acquired loss of heterozygosity – for example, due to monosomy 7 or uniparental disomy 7 – often occurs in hematopoietic tissue of individuals with a pathogenic *SAMD9* variant. *SAMD9* is located on chromosome 7 and loss of chromosomes with a pathogenic *SAMD9* variant occurs preferentially [Narumi et al 2016].

This somatic change results in a decreased proportion of hematopoietic cells with the variant and may cause a false negative molecular result when testing leukocyte DNA. Therefore, evaluation of genomic abnormalities with SNP array and/or evaluation of low-abundance variants with deep sequencing (>1000X read depth) should be considered in individuals clinically suspected for MIRAGE syndrome who have a negative genetic test result. If feasible, use of DNA derived from non-hematopoietic tissues (e.g., skin fibroblasts, hair roots) may be considered.

Table 7. Notable *SAMD9* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_017654.4 NP_060124.2	c.1376G>A	p.Arg459Gln	Found in 4 unrelated persons [Narumi et al 2016, Buonocore et al 2017, Yoshizaki et al 2019]
	c.2920G>A	p.Glu974Lys	Found in 4 unrelated persons [Narumi et al 2016, Sarthy et al 2018, Zhang et al 2019, Mengen et al 2020]
	c.2944C>T	p.Arg982Cys	Found in 3 unrelated persons [Buonocore et al 2017, Kim et al 2018]
	c.3878G>A	p.Arg1293Gln	Found in 3 unrelated persons [Buonocore et al 2017, Jeffries et al 2018, Viaene & Harding 2020]

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

Author Notes

National Research Institute for Child Health and Development –
MIRAGE syndrome web page

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