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NLM Citation: Priolo M. *NFIX*-Related Malan Syndrome. 2024 Aug 1. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

NFIX-Related Malan Syndrome

Synonyms: Sotos-Like Syndrome, Sotos Syndrome 2

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Created: August 1, 2024.

Summary

Clinical characteristics

NFIX-related Malan syndrome (MALNS) is characterized by prenatal and postnatal overgrowth, macrocephaly, advanced bone age and/or skeletal anomalies (scoliosis, pes planus), slender body habitus, developmental delay / intellectual disability (typically in the moderate-to-severe range), behavioral problems (including a specific anxious profile and attention-deficit/hyperactivity disorder [ADHD]), and ocular findings (most commonly strabismus, refractive errors, and blue sclerae). Affected individuals typically have distinctive facial features, including a long and triangular face, high anterior hair line with prominent forehead, depressed nasal bridge, deep-set eyes, downslanted palpebral fissures, short nose with anteverted nares and upturned tip, long philtrum, small mouth that is often held open, thin vermilion of the upper lip, an everted lower lip, and a prominent chin. Other findings may include autonomic signs (episodic ataxia with dizziness and nausea and/or postural fainting), seizures or EEG abnormalities, hypotonia, dental anomalies, long bone fractures, and (rarely) congenital heart defects. Four individuals with aortic root dilatation have been reported, with one adult individual experiencing progressive aortic dilation and dissection at age 38 years. Additionally, one individual with rib osteosarcoma and another with Wilms tumor have been reported (an overall prevalence of malignancy of about 2%). Therefore, MALNS appears to be in the same low risk group as Sotos syndrome and Weaver syndrome with respect to a low likelihood of developing cancer.

Diagnosis/testing

The diagnosis of MALNS is established in a proband with suggestive findings and either a heterozygous pathogenic variant in *NFIX* (~75% of affected individuals) OR a heterozygous deletion of 19p13.2 that includes *NFIX* (~25% of affected individuals) identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy with a low threshold for clinical feeding evaluation &/or radiographic swallowing study for those with clinical signs or symptoms of dysphagia; gastrostomy tube placement may be required for persistent feeding issues. Stool softeners, prokinetics, osmotic agents, or laxatives

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as needed for constipation. Symptomatic treatment for autonomic signs based on the underlying cause. Cognitive behavioral therapy (CBT) may be used to treat anxiety and ADHD. Symptomatic aids (i.e., colored glasses, low voice tone) may reduce anxiety outbursts. Hearing aids may be helpful per otolaryngologist. Standard treatment for epilepsy, Chari I malformation, developmental delay / intellectual disability, scoliosis/kyphosis, pes planus, pectus anomalies, refractive error, strabismus, tooth anomalies / malocclusion, aortic root dilatation / valvular issues, and cryptorchidism.

Surveillance: At each visit, measure growth parameters and evaluate nutritional status and safety of oral intake; monitor for signs/symptoms of constipation, Chari I malformation, and subtle and nonspecific neurovegetative findings; and assess for new manifestations, such as seizures and changes in tone. The first BMI evaluation should be performed after age two years; assess caloric intake and BMI every six months during the first two years of life, then at least annually. Monitor developmental progress, educational needs, and psychopathologic symptoms annually from age 12 months to age 36 months and then approximately every two years from age three to six years. Annual ophthalmology evaluation until puberty and then periodically in adults to evaluate for late-onset optic nerve degeneration. Annual audiology evaluation in childhood or as clinically indicated. At least annual routine dental/orthodontic evaluation. Consider DXA scan for bone mineral density periodically in those with a history of multiple fractures or previous low bone mineral density. If the baseline cardiovascular evaluation is normal, consider annual cardiology follow up; limited data on aortic root progression is available for adults. No tumor screening protocols have been proposed or recommended for individuals with MALNS.

Genetic counseling

MALNS is an autosomal dominant disorder typically caused by a *de novo* genetic alteration. Therefore, the risk to other family members is presumed to be low. Rarely, individuals diagnosed with MALNS have the disorder as the result of a genetic alteration inherited from a mosaic parent. Families with sib recurrence due to parental gonadal (or somatic and gonadal) mosaicism have been reported. Once an *NFIX* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *NFIX*-related Malan syndrome (MALNS) have been published.

Suggestive Findings

MALNS **should be suspected** in individuals with at least five out of the following eight features [Priolo et al 2018, Mulder et al 2020, Alfieri et al 2022, Macchiaiolo et al 2022]:

- Prenatal overgrowth, often with a diagnosis of being large for gestational age
- Postnatal overgrowth (length/height and/or head circumference ≥2 standard deviations [SD] above mean for age and sex)
- Developmental delay / intellectual disability
- Behavioral problems
- Distinctive facial features (See Clinical Description.)
- Advanced bone age and/or skeletal anomalies, such as scoliosis, pes planus, and pectus anomaly
- Slender body habitus
- Ocular findings, most commonly strabismus, refractive errors, and blue sclerae

Family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of MALNS **is established** in a proband with suggestive findings and one of the following on molecular genetic testing (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant in *NFIX* (~75% of affected individuals)
- A heterozygous deletion of 19p13.2 that includes *NFIX* (~25% of affected individuals)

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 can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *NFIX* 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** (chromosomal microarray analysis, 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 overgrowth and/or intellectual disability are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *NFIX* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. 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.
- **An overgrowth multigene panel** that includes *NFIX* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by overgrowth and intellectual disability, comprehensive genomic testing may be considered. **Chromosomal microarray (CMA)** may be performed first.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *NFIX*) that cannot be detected by sequence analysis.

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

- If CMA is not diagnostic, **exome sequencing** is often performed next; alternatively, **genome sequencing** may be considered instead of CMA and exome testing.

Table 1. Molecular Genetic Testing Used in *NFIX*-Related Malan Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
NFIX	Sequence analysis [3]	~70% [4]
	CMA [5]	~25%-28% [6]
	Gene-targeted deletion/duplication analysis [7]	An additional ~2%-5% [8]

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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Priolo et al [2018], Priolo et al [2019], Langley et al [2022], Macchiaiolo et al [2022]
5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *NFIX*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 19p13.2 region. Typically, single-exon deletions or duplications are below the resolution of CMA detection (see footnote 6).
6. Auvin et al [2009], Lysy et al [2009], Bonaglia et al [2010], Dolan et al [2010], Nimmakayalu et al [2013], Natiq et al [2014], Klaassens et al [2015], Shimojima et al [2015], Dong et al [2016], Jezela-Stanek et al [2016], Kuroda et al [2017], Priolo et al [2018], Bellucco et al [2019], Macchiaiolo et al [2022]
7. 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene.
8. Gene-targeted deletion/duplication analysis may be useful to detect an additional 2%-5% of partial-gene deletions [M Priolo, personal observation; Sanford CoRDS patient registry for Malan syndrome]. However, it should be noted that targeted deletion/duplication analysis should also be able to detect any chromosomal deletion that includes *NFIX* and surrounding genes (although it cannot identify the size or gene content of contiguous deletions that include *NFIX* and other genes). Therefore, the total detection rate of gene-targeted deletion/duplication analysis is around 27%-30%.

Clinical Characteristics

Clinical Description

NFIX-related Malan syndrome (MALNS) was first reported in three individuals with overgrowth and heterozygous pathogenic variants in *NFIX* in 2010 [Malan et al 2010]. Since that time, at least 100 individuals have been identified with MALNS [Priolo et al 2012, Yoneda et al 2012, Klaassens et al 2015, Gurrieri et al 2015, Martinez et al 2015, Jezela-Stanek et al 2016, Oshima et al 2017, Priolo et al 2018, Hancarova et al 2019, Sihombing et al 2020, Tabata et al 2020, Langley et al 2022, Macchiaiolo et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *NFIX*-Related Malan Syndrome: Frequency of Select Features

System	Feature	% of Persons w/Feature [1]	Comment
Facial	Distinctive facial features	100%	
Growth	Macrocephaly	100%	77% of adults maintain a head circumference >2 SD above mean.
	Postnatal length/height >2 SD above mean	56%	Final adult height falls w/in 2 SD of mean in two thirds of affected persons.
Neurologic	Developmental delay / intellectual disability	100%	May vary from moderate to severe
	Hypotonia	65%	
	Epilepsy / EEG anomalies	10/16 (63%) [2]	Persons w/contiguous deletion incl *NFIX* & surrounding genes have higher risk of epilepsy compared to those w/ intragenic *NFIX* pathogenic variant.
	Autonomic signs	4/16 (25%) [2]	Incl episodic ataxia w/dizziness & nausea &/or postural fainting
	Neurobehavioral/psychiatric manifestations	12/14 (86%) [2, 3]	10/15 (67%) [2] showed hypersensitivity to noise. [3]
Musculoskeletal	Slender body habitus	16/16 (100%) [2]	
	Advanced bone age	76%	
	Abnormal spine curvature	12/16 (75%) [2]	
	Pectus carinatum, excavatum, or mixed	10/16 (63%) [2]	
	Pes planus	11/16 (69%) [2]	
	Long hands & fingers	10/16 (63%) [2]	
	Long bone fractures	5/16 (31%) [2]	
Eye	Refractive errors	75%	
	Strabismus	10/16 (63%) [2]	
	Esotropia	9/16 (56%) [2]	
	Nystagmus	5/16 (31%) [2]	
	Blue sclerae	11/16 (69%) [2]	Mainly persisting after infancy
	Cataract	2/16 (13%) [2]	Mainly polar posterior cataract
	Optic nerve hypoplasia	25%	
Cardiovascular	Cardiovascular anomalies	4%	Low-grade mitral regurgitation is most common finding; [4] other CHD & aortic root dilatation are less common but require assessment & monitoring (see Management).
Mouth	Malocclusion	7/16 (44%) [2]	
	Ogival (narrow) palate / dental crowding	9/16 (56%) [2]	
	Dental caries	6/16 (38%) [2]	
	Oral apraxia / hypersalivation	31% (5/16) [2]	

Table 2. continued from previous page.

System	Feature	% of Persons w/Feature [1]	Comment
Other	Constipation	50% (8/16) [2]	
	Hepatomegaly	25% (4/16) [2]	
	Low BMI	38% (6/16) [2]	
	Cryptorchidism	13% (2/16) [2]	
	Hearing loss	2%	Of the 2 reported persons w/this finding, both had sensorineural hearing loss.

Adapted from Priolo et al [2018] and Macchiaiolo et al [2022]
BMI = body mass index; CHD = congenital heart defects; SD = standard deviations
1. Percentages refer to individuals with a pathogenic variant in *NFIX*. These frequencies may vary slightly in individuals who have a continuous gene deletion involving *NFIX*, although this is not significant except where noted [Priolo et al 2018]; see also Genotype-Phenotype Correlations.
2. When a fraction is specified, the percentage refers to a specific cohort of affected individuals who underwent a deep phenotyping analysis by an experienced team [Macchiaiolo et al 2022].
3. Alfieri et al [2023]
4. Low-grade mitral valve regurgitation has been recorded in at least one third of individuals. However, this data should be considered a minor anomaly and not sufficient to classify MALNS as a condition predisposing to cardiovascular disease and/or heart anomalies.

Facial features. Distinctive facial features are generally present in all affected individuals identified to date. The facial features include a long and triangular face, high anterior hair line with prominent forehead, depressed nasal bridge, deep-set eyes, downslanted palpebral fissures, short nose with anteverted nares and upturned tip, long philtrum, small mouth that is often held open, thin vermilion of the upper lip, an everted lower lip, and a prominent chin (see Figure 1). Other less frequent features are high-arched palate, dental crowding, sparse hair, loose and soft skin, and facial asymmetry [Priolo et al 2018, Alfieri et al 2022, Macchiaiolo et al 2022].

Growth

- **Macrocephaly** is observed in all reported individuals to date [Priolo et al 2018, Priolo 2019, Macchiaiolo et al 2022]. Dolichocephaly is also usually present.
  - Approximately 41% of newborns with MALNS have a head circumference >2 standard deviations (SD) above the mean for sex.
  - At least 77% of adults maintain a head circumference >2 SD above the mean for sex.
- **Prenatal and postnatal overgrowth**
  - About 15% of affected newborns will be characterized as large for gestational age (weight at birth >2 SD above the mean for sex), but weight is reported to be above the mean for about 90% of affected newborns.
  - Postnatal overgrowth is generally recognized in childhood and adolescence, with a length/height >2 SD above the mean for age and sex reported in 56% of affected individuals.
  - About one third of affected individuals' final adult height is >2 SD above the mean [Priolo et al 2018, Priolo et al 2019, Macchiaiolo et al 2022].
- **Body mass index (BMI)** falls <2 SD below the mean for age and sex in at least one third of affected individuals, despite normal micro- and macronutrient intake for age [Macchiaiolo et al 2022]. This finding may be due to the overall slender body habitus (see **Musculoskeletal** below).

Developmental delay (DD) and intellectual disability (ID). Cognitive impairment and DD are invariably present and may range from moderate to severe. Rarely, mild ID has been reported.

- Typically, affected individuals show both low cognitive and adaptive functioning, with communication skills being the most affected.
- The level of intellectual impairment generally remains stable throughout life.
- A dedicated diagnostic battery of tests has been proposed to carefully assess the impairment in different domains (for a full review of the battery of tests recommended, see Alfieri et al [2022] and Alfieri et al [2023]).
- Aadaptive functioning is usually lower than normal, generally ranging from moderately to severely impaired, with communication skills the most affected.
- Verbal language skills are usually the most severely impacted, with receptive language more preserved than expressive language [Mulder et al 2020, Alfieri et al 2022, Alfieri et al 2023].

Other neurodevelopmental features

- **Hypotonia.** At least 65% of individuals with MALNS have been reported to have hypotonia. This finding may cause, together with DD, feeding difficulties and drooling in infancy. Hypotonia may persist during childhood and slowly improve with time.
- **Autonomic findings.** Recurring autonomic signs have been reported in at least 25% of affected individuals. Symptoms may be subtle or nonspecific (e.g., vomiting/nausea, dizziness, fainting). These signs may be occasional or triggered by external causes (stress, anxiety, provoking situations).

  The same signs, sometimes associated with gait disturbances (e.g., broad-based gait, toe-walking), have also been occasionally described in affected individuals with Chiari I malformations, but they may be also observed in individuals with MALNS who do not have Chiari I malformations. For this reason, individuals with MALNS should be first assessed for Chiari I malformations through neuorimaging and then for other causes (e.g., cardiac/otologic evaluation) of these nonspecific symptoms.

Epilepsy. Seizures and electroencephalogram (EEG) anomalies are common and more frequently observed among individuals with continuous gene deletions that include *NFIX* and surrounding genes. Individuals with *NFIX* intragenic pathogenic variants are prone to develop nonspecific EEG anomalies, which usually do not require anti-seizure medication (ASM) [Macchiaiolo et al 2022]. The exact types and severity of epilepsy in individuals with this condition have not been well characterized to date.

Neurobehavioral/psychiatric manifestations affect most individuals with MALNS. Behavioral problems characterized by a specific anxious profile are seen in more than 80% of affected individuals. Anxiety does not appear to affect individuals in any specific age range but may worsen over time.

The most prevalent psychiatric comorbidities include generalized anxiety disorder; separation anxiety with specific phobias; attention-deficit/hyperactivity disorder; and behavioral issues (e.g., impaired socialization) that may resemble those of individuals with autism but are different from classic autistic behavior.

Some affected individuals may be given a clinical diagnosis of an autism spectrum disorder primarily because of their expressive language difficulties. However, most affected individuals do not have true impairment in social interactions outside of their deficient communication skills [Mulder et al 2020, Alfieri et al 2022, Alfieri et al 2023].

Additional neuropsychiatric hallmarks include difficulty with visuomotor integration; hypersensitivity to visual and auditory stimuli (noise hypersensitivity and photophobia), both of which may contribute to psychopathology; and challenging behaviors with panic crises and, rarely, outbursts of hetero-aggression and self-injurious behavior.

Neuroimaging. Brain MRI abnormalities are identified in at least half of individuals with MALNS. Ventricular dilatation and corpus callosum hypoplasia are the most frequent findings, present in 8/16 (50%) individuals

reported by Macchiaiolo et al [2022]. Chiari I malformation has been identified in 6/16 (38%) affected individuals. In the study by Macchiaiolo et al [2022], about 25% of affected individuals had various degrees of optic nerve hypoplasia; however, data from patient registries suggest that this latter figure might be an underestimate [Sanford CoRDS patient registry for Malan syndrome].

Musculoskeletal features may include the following:

- Slender body habitus (almost all individuals)
- Advanced bone age (at least 76%)
- Scoliosis (75%)
- Hyperkyphosis or hyperlordosis (~30%)
- Pes planus (69%)
- Pectus anomaly (excavatum, carinatum, or mixed) (63%)
- Long bone fracture
    - Individuals with MALNS have a slightly increased risk of bone fractures during childhood as compared to the general population [Macchiaiolo et al 2022].
    - Rarely, mild osteopenia has been identified by DXA scan, which quickly resolved after vitamin D_3 supplementation (see Management) [Macchiaiolo et al 2022, Sanford CoRDS patient registry for Malan syndrome].

Ophthalmologic findings, including strabismus and refractive errors (such as myopia, hypermetropia, and astigmatism), occur with an overall frequency of about 75%. About 70% of affected individuals have blue sclerae. There is some evidence to suggest that adults with MALNS may be at risk for late-onset optic nerve degeneration. Other findings may include:

- Nystagmus (31%)
- Polar posterior cataract (13%)
- Optic nerve hypoplasia and optic disk pallor (25%)

Cardiovascular anomalies have been reported in a small proportion of individuals with MALNS. Four individuals with aortic root dilatation and one with pulmonary artery dilatation have been reported [Nimmakayalu et al 2013, Oshima et al 2017, Priolo et al 2018]. There is limited data available on aortic root z scores or on whether aortic dilation was static or progressive; however, one affected adult experienced progressive aortic dilation and dissection at age 38 years [Oshima et al 2017]. Minor cardiac anomalies, such as low-grade mitral regurgitation, have been frequently observed [Macchiaiolo et al 2022]. Other major cardiac findings have been reported in a minority of reported individuals.

Gastrointestinal issues. Isolated hepatomegaly has been observed in about one quarter of individuals with MALNS either during childhood or adulthood. It is not generally associated with liver dysfunction.

Different degrees of constipation, sometimes requiring pharmacologic therapy (see Management), have been observed in almost half of individuals.

Hearing. Two individuals with MALNS have been reported with bilateral moderate-to-severe sensorineural hearing impairment [Priolo et al 2018, Sanford CoRDS patient registry for Malan syndrome]. Many individuals with this condition are sensitive to noise (see **Neurobehavioral/psychiatric manifestations** above).

Genitourinary. A minority of affected males have had cryptorchidism. Renomegaly might be observed as an incidental finding.

Malignancy. To date, one individual with rib osteosarcoma and another with Wilms tumor have been reported (an overall prevalence of malignancy of about 2%). Therefore, MALNS appears to be in the same low risk group as Sotos syndrome and Weaver syndrome with respect to a low likelihood of developing cancer [Villani et al

2017, Priolo et al 2018, Brioude et al 2019, Macchiaiolo et al 2022]. Therefore, no tumor screening protocols have been proposed or recommended for individuals with MALNS.

Prognosis. It is unknown whether the life span in MALNS is abnormal. Two reported individuals are alive at age 40 and 60 years, respectively [M Priolo, personal observation], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Deletion of 19p13.2. At least 25% of individuals with MALNS have a deletion of the 19p13.2 region that includes *NFIX* and other adjacent genes. There is no significant difference in growth pattern, cognitive impairment, facial characteristics, or skeletal manifestations in those with larger deletions that include *NFIX* compared to those with intragenic *NFIX* pathogenic variants. However, individuals with a deletion containing *NFIX* and adjacent genes are more likely to have seizures and EEG abnormalities compared to those with intragenic *NFIX* pathogenic variants, which may be due to deletion of *CACNA1A*, which is located about 109 kilobases (kb) from *NFIX* [Priolo et al 2018].

***NFIX* intragenic pathogenic variants.** There are no significant genotype-phenotype correlations for individuals with intragenic *NFIX* pathogenic variants (see Molecular Genetics). MALNS-associated frameshift pathogenic variants are expected to produce mRNA that undergoes nonsense-mediated decay (NMD) [Priolo et al 2018]. In contrast to this, Marshall-Smith syndrome-associated mutated mRNA typically is not predicted to undergo NMD [Malan et al 2010; Schanze et al 2014] (see Genetically Related Disorders).

Nomenclature

NFIX-related Malan syndrome (MALNS) has previously been referred to as Sotos syndrome 2. This term is now outdated and should no longer be used.

Prevalence

Based on the number of known affected individuals, the prevalence of *MALNS* is estimated to be about 1:1,000,000 [Macchiaiolo et al 2022]. However, data from association registries strongly support that the exact prevalence of the condition is highly underestimated [M Priolo, unpublished data; Sanford CoRDS patient registry for Malan syndrome].

Genetically Related (Allelic) Disorders

Heterozygous pathogenic variants in *NFIX* have also been described in individuals with Marshall-Smith syndrome.

Marshall-Smith syndrome (MSS) (OMIM 602535) is characterized by unusual facial features, distinctive dysostosis, postnatal poor growth with ultimate short stature, respiratory insufficiency, and moderate-to-severe developmental delay / intellectual disability [Marshall et al 1971, Adam et al 2005, Shaw et al 2010, van Balkom et al 2011, Schanze et al 2014, Priolo et al 2019]. Individuals with MSS differ markedly in growth pattern compared to individuals with *NFIX*-related Malan syndrome (MALNS), both prenatally and postnatally. MALNS and MSS are two separate clinical entities, although individuals with some phenotypic overlap do exist [Priolo et al 2018]. Individuals with MSS may be distinguished from those with MALNS by the absence of macrocephaly and the presence of proptosis, underdeveloped midface, and small chin in MSS. Some facial findings, such as a prominent forehead, short nose with anteverted nares, and everted lower lip, are present in individuals with both conditions, although generally more pronounced in individuals with MSS. A slender habitus and sternum abnormalities are uncommon in individuals with MSS. Scoliosis is common in individuals

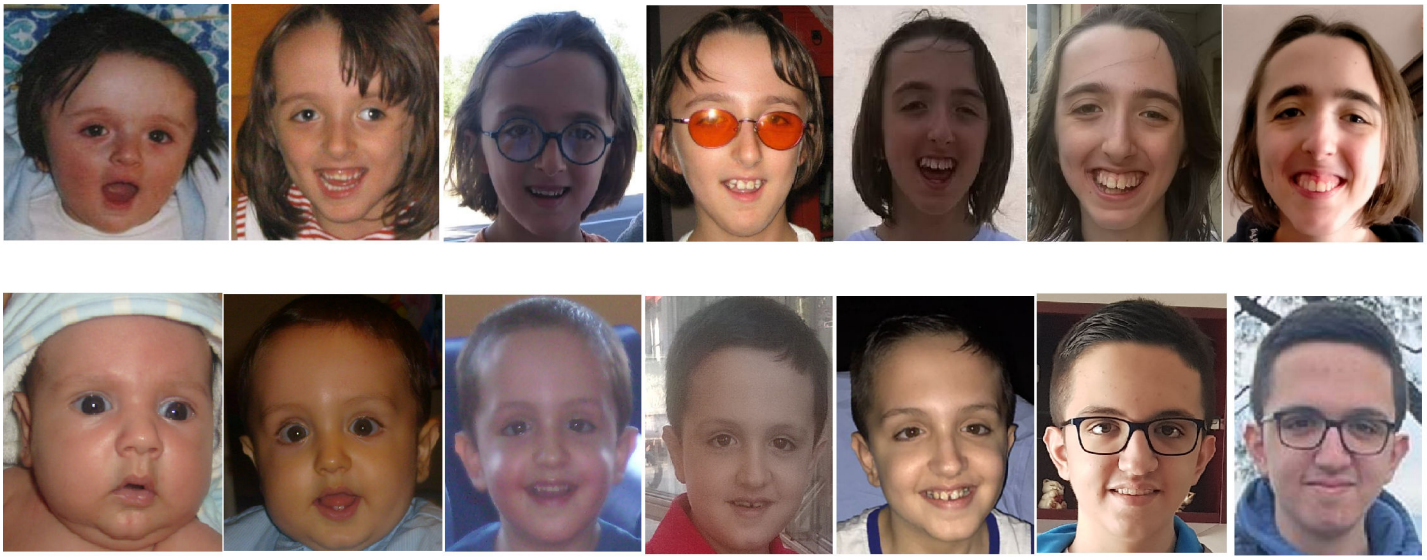

Figure 1. Clinical features of individuals with Malan syndrome at different ages, with evolving facial appearance. Note long and triangular face, high anterior hair line with prominent forehead, downslanted palpebral fissures, small mouth, everted lower lip, and prominent chin.

Reproduced from Macchiaiolo et al [2022]

with both conditions, although scoliosis is more typically severely progressive in individuals with MSS. Hypertrichosis and gum hypertrophy are almost completely limited to individuals with MSS [Priolo et al 2018, Priolo et al 2019].

Typically, truncating pathogenic variants affecting exons 6-10 of *NFIX* cause MSS, generating a different mRNA product as compared to individuals with MALNS. Despite the rare overlap in the genomic positions of some pathogenic variants in those with MSS versus those with MALNS, the alignment of the corresponding mutated protein is typically predictive of which phenotype (MSS vs MALNS) will be present [Priolo et al 2018, Priolo et al 2019]. MSS-associated mutated mRNA does not undergo NMD [Malan et al 2010, Schanze et al 2014]. Although the pathogenesis of the MSS-associated pathogenic variants appears to be related to the generation of expressed mutated protein that contains conserved DNA binding capacity, it remains possible that these mutated proteins might also have aberrant functions mediated by their altered C terminus [Priolo et al 2018, Priolo et al 2019].

Differential Diagnosis

Sotos syndrome (SS), a syndromic overgrowth condition, is the primary differential diagnosis of *NFIX*-related Malan syndrome (MALNS). SS and MALNS are phenotypically similar and have overlapping clinical presentations but are distinguished by significant differences in the severity and frequency of several key features.

- **Developmental delay (DD) and intellectual disability (ID)** are usually more severe in individuals with MALNS than in individuals with SS. This difference is more evident when comparing affected adult populations. At least one third of individuals with SS have been reported to have normal intellectual development or mild ID [Foster et al 2019], while normal intellectual development has never been reported in MALNS and mild ID is rarely observed [Alfieri et al 2022, Macchiaiolo et al 2022, Alfieri et al 2023].
- **Behavior and psychiatric issues.** Although the spectrum of behavior and psychiatric issues in MALNS and SS (e.g., anxiety, autistic or autism-like behavior, anger/aggressive behavior) may be largely

overlapping [Lesinskiene et al 2024], some of these features (e.g., generalized anxiety disorder, separation anxiety with specific phobias, impaired socialization) are reported less frequently in individuals with SS than in individuals with MALNS [Alfieri et al 2022, Macchiaiolo et al 2022, Alfieri et al 2023, Huynh et al 2024].

- **Severe ophthalmologic anomalies with vision impairment** (e.g., optic nerve hypoplasia or optic nerve atrophy) are more common in MALNS than in SS [Inoue et al 2000, Nalini & Biswas 2008].
- **Musculoskeletal anomalies.** With the exception of scoliosis (which is present in about 30% of individuals with SS), musculoskeletal anomalies generally occur less frequently and are less severe in SS.
- **Body mass index (BMI).** Unlike MALNS – in which almost all individuals have a slender body habitus and the BMI falls <2 SD below the mean for age and sex in at least one third of affected individuals – a low BMI is rarely observed in individuals with SS.

See Table 3 for additional disorders in the differential diagnosis of MALNS. (Note: With the exception of *FBN1*-related Marfan syndrome, all the disorders in Table 3 are characterized by variable degrees of DD and/or ID.)

Table 3. Genes of Interest in the Differential Diagnosis of *NFIX*-Related Malan Syndrome

Gene	Disorder [1]	MOI	Features of Disorder	
			Overlapping w/MALNS [2]	Distinguishing from MALNS
NSD1	Sotos syndrome	AD [3]	See **Sotos syndrome** above.	See **Sotos syndrome** above.
EZH2	*EZH2*-related Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD [3]	• Generalized prenatal & postnatal overgrowth • Macrocephaly, long philtrum, retrognathia (usually resolves w/ age), & prominent chin crease	• Round face, increased bifrontal diameter • Flattened occipitus
SUZ12	*SUZ12*-related overgrowth syndrome (Imagawa-Matsumoto syndrome) (OMIM 618786)	AD	• Generalized prenatal & postnatal overgrowth • Macrocephaly • Hypertelorism, downslanting palpebral fissures • Hypotonia • Agenesis of corpus callosum, enlargement of cerebral ventricles	• Distinctive facial features more resembling Weaver syndrome • Although large hands & feet have been reported, arachnodactyly has not been described.
EED	*EED*-related overgrowth	AD [3]	• Scoliosis • Ligamentous hyperlaxity • Neonatal hypotonia	Distinctive facial features more resembling Weaver syndrome
SETD2	Luscan-Lumish syndrome (See *SETD2* Neurodevelopmental Disorders.)	AD [3]	• Generalized prenatal & postnatal overgrowth • Macrocephaly • Long face, downslanting palpebral fissures, pointed chin • Speech delay • Anxiety disorder, behavioral difficulties incl ASD &/or outbursts of aggression • Chiari I malformation, ventriculomegaly	• Malar hypoplasia • Hyperphagia • Seizures are reported more frequently than in MALNS.

Table 3. continued from previous page.

Gene	Disorder [1]	MOI	Features of Disorder	
			Overlapping w/MALNS [2]	Distinguishing from MALNS
MED12	Lujan syndrome (See *MED12*-Related Disorders.)	XL	• Marfanoid habitus, pectus excavatum, long fingers • High-arched palate, prominent forehead, long face • Macrocephaly • Ascending aortic aneurysm • Behavioral manifestations (Affected persons are commonly hyperactive, aggressive, shy, & attention seeking.)	• Low-set ears, long nose, high & narrow nasal bridge • Seizures are reported more frequently than in MALNS.
CBS	Homocystinuria caused by cystathionine beta-synthase deficiency (classic homocystinuria)	AR	• Marfanoid habitus, kyphoscoliosis, pectus excavatum/carinatum, arachnodactyly • High-arched palate • Psychiatric problems incl personality disorder, anxiety, depression, obsessive-compulsive behavior, & psychotic episodes	• Ectopia lentis, glaucoma • Thromboembolism • Seizures are reported more frequently than in MALNS. • Homocystinuria, methioninuria, cystathionine beta-synthase deficiency
SMS	Snyder-Robinson syndrome	XL	• Marfanoid habitus, pectus excavatum/carinatum, kyphoscoliosis, arachnodactyly • High, narrow palate • Multiple fractures	• Facial asymmetry, asymmetric dysplastic ears • Short, webbed neck • Seizures are reported more frequently than in MALNS.
FBN1	*FBN1*-related Marfan syndrome	AD	• Marfanoid habitus, pectus excavatum/carinatum, kyphoscoliosis, arachnodactyly • High-arched palate, downslanting palpebral fissures • ↓ subcutaneous fat	• Ectopia lentis, retinal detachment, glaucoma • Aortic root dilatation/aneurism/dissection • No DD/ID

AD = autosomal dominant; AR= autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MALNS = *NFIX*-related Malan syndrome; MOI = mode of inheritance; XL = X-linked

1. Rows are ordered by degree of phenotypic overlap with MALNS; disorders with the most phenotypic overlap are listed first.

2. In addition to DD/ID (with the exception of *FBN1*-related Marfan syndrome)

3. Many affected individuals have a *de novo* pathogenic variant.

Management

Suggested management and follow up recommendations for individuals with *NFIX*-related Malan syndrome (MALNS) have been published [Alfieri et al 2022, Macchiaiolo et al 2022, Alfieri et al 2023].

Evaluations Following Initial Diagnosis

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

Table 4. *NFIX*-Related Malan Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for macrocephaly & postnatal overgrowth
	Calculate BMI & calorie intake.	In those age >2 years
Gastrointestinal/ Feeding	Assess dietary intake & variety of foods eaten.	• Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk. • If BMI is >2 SD below mean for age & sex, reevaluate appropriateness of reported caloric intake.
	Assess for signs/symptoms of constipation.	
	Physical exam	• To screen for hepatomegaly, although most hepatomegaly described to date has not been assoc w/liver dysfunction • Consider abdominal ultrasound if hepatomegaly is suspected by physical exam.
Neurologic	Neurologic eval, incl for signs/symptoms of Chiari I malformation [1]	Brain MRI should be considered for those w/concerning symptoms of Chiari I malformation or in those w/seizures.
	Assess for signs/symptoms of seizures.	• Consider EEG if seizures are a concern. • In absence of clinical seizures, a watch & wait strategy is reasonable if EEG demonstrates nonspecific changes, esp in those w/intragenic *NFIX* pathogenic variant (see Table 6).
	Assess for autonomic signs.	• Such as vomiting/nausea, dizziness, & fainting • If present, assessment for potential causes (Chiari I malformation, cardiac, otolaryngologic) is indicated. • Consider possible triggering events.
Development	Developmental assessment	• Incl complete motor, adaptive, cognitive, & speech-language eval [2] • Eval for early intervention / special education services
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	• Define cognitive & adaptive behavior profile. • Verify visuomotor abilities, noise hypersensitivity, & photophobia.
Musculoskeletal	Incl assessment for: • Gross motor & fine motor skills • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Kyphoscoliosis • Pes planus • Pectus excavatum/carinatum • History of frequent fractures	• In those w/severe pectus anomalies, consider overnight pulse oximetry test. • Consider baseline DXA scan around time of puberty or if person sustains multiple fractures. • Consider referral to orthopedist. • Consider referral to endocrinologist.
Eyes	Ophthalmologic eval	• To assess for refractive errors, nystagmus, strabismus, polar cataract, & optic disk pallor • Consider VEP & ERG to assess conduction in visual pathway.
Hearing	Audiologic eval	Assess for hearing loss.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
ENT/Mouth	Incl assessment for: • Narrow (ogival) palate • Tooth overgrowth • Malocclusion • Dental caries	Consider referral to dentist &/or orthodontist.
Cardiovascular	Consider echocardiogram to assess for aortic root indices & minor valvular issues.	Consider referral to cardiologist.
Genitourinary	Assessment for cryptorchidism in males	Consider referral to urologist
	Perform renal ultrasound to look for kidney enlargement.	Renomegaly may be identified but typically does not lead to clinical kidney disease.
Genetic counseling	By genetics professionals [3]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of MALNS to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

BMI = body mass index; DXA = dual-energy x-ray absorptiometry; ERG = electroretinogram; MALNS = *NFIX*-related Malan syndrome; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SD = standard deviations; VEP = visual evoked potential

1. Which may include severe headaches, neck pain, poor balance, dizziness, numbness or tingling in the hands/feet, and/or swallowing issues

2. See Alfieri et al [2022] and Alfieri et al [2023].

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

Treatment of Manifestations

There is no cure for MALNS. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *NFIX*-Related Malan Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1] • Persons w/o clinical signs of seizures who have nonspecific EEG changes may not require medical therapy [2] (see Table 6).

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Chari I malformation	Standard treatment per neurosurgeon	
Autonomic signs	Symptomatic treatment, which may be based on underlying cause (See Table 4.)	Education of parents/caregivers to avoid triggering causes (stress, anxiety-provoking situations)
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Neurobehavioral/ Psychiatric	• Cognitive behavioral therapy to treat anxiety & ADHD • Standard treatment for visuomotor abilities, photophobia, & noise sensitivity • Symptomatic aids (i.e., colored glasses, low voice tone) may reduce anxiety ↓. • Consider introducing AAC when expressive language difficulties are a concern.	The association of ID, verbal communication deficits, & sensory abnormalities may lead affected persons to display autistic behaviors & social withdrawal.
Scoliosis/ Kyphosis	Standard treatment per orthopedist, which may incl bracing or surgery	Scoliosis &/or kyphosis may vary from mild to severe.
Pes planus	Standard treatment per orthopedist	
Pectus deformities	Standard treatment per orthopedist	In general, pectus deformities do not require surgical correction.
Eyes	Standard treatment per ophthalmologist	For refractive errors, strabismus
	Standard treatment per ophthalmologic subspecialist	For more complex findings (e.g., optic atrophy)
Hearing	Hearing aids may be helpful per otolaryngologist	Community hearing services through early intervention or school district
Tooth anomalies / Malocclusion	Standard treatment per dentist &/or orthodontist	
Aortic root dilation / Valvular issues	Standard treatment per cardiologist	
Cryptorchidism	Standard treatment per urologist	
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 palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

AAC = augmentative alternative communication; ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; ID = intellectual disability

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

2. Particularly in individuals with an intragenic *NFIX* pathogenic variant. Individuals with a deletion that includes *NFIX* and adjacent genes may have a greater chance of developing seizures compared to those with an intragenic *NFIX* pathogenic variant (see Genotype-Phenotype Correlations).

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 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).

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.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder (ASD), including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary. Cognitive behavioral therapy (CBT) has been proven effective in treating anxiety disorders, ASD, and ADHD; therefore, early initiation of CBT should be considered in those with adequate cognitive skills.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist. However, any drug therapy to treat psychiatric symptoms should be weighed against the age of the affected person (child or adolescent) and the specific medical comorbidities of individuals with MALNS, with close consideration for possible current or future drug interactions that may be given to treat MALNS-specific medical issues.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *NFIX*-Related Malan Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Constitutional/ Growth/Nutrition	Measurement of growth parameters	• At each visit • 1st BMI eval should be performed after age 2 yrs.
	Assessment of caloric intake & BMI (in those age >2 yrs) [1]	Every 6 mos during 1st 2 yrs of life, then at least annually

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Gastrointestinal/ Feeding	• Eval of nutritional status & safety of oral intake • Assessment for signs/symptoms of constipation	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as changes in tone, signs/symptoms of Chari I malformation, [2] & seizures. [3] • Assess for subtle & nonspecific autonomic signs/symptoms. [4]	
Developmental/ Neurobehavioral/ Psychiatric	Monitor developmental progress, educational needs, & psychopathologic symptoms.	• From age 12 mos to approximatively 36 mos: annually • From age 3 yrs to adulthood: every 2 yrs
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, presence or progression of scoliosis/kyphosis, pes planus, & pectus anomaly	At each visit
	Consider DXA eval for bone mineral density.	Periodically in those w/history of multiple fractures & ↓ bone mineral density on previous DXA eval
Eyes/Vision	Ophthalmology eval	• Annually until puberty • Periodic eval should be performed in adults to evaluate for late-onset optic nerve degeneration.
Hearing	Audiology eval	Annually in childhood or as clinically indicated
ENT/Mouth	Routine dental/orthodontic evals	At least annually
Cardiovascular	Cardiology eval, w/consideration of echocardiogram	If baseline eval is normal, consider annual cardiology follow up. Limited data on aortic root progression is available for adults.
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

BMI = body mass index; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

1. Those with a BMI of >2 standard deviations below the mean require reassessment of their caloric intake and the appropriateness of their food intake.

2. Including severe headaches, neck pain, poor balance, dizziness, numbness or tingling in the hands/feet, and/or swallowing issues

3. Individuals with a deletion that includes *NFIX* and adjacent genes may have a greater chance of developing seizures compared to those with an intragenic *NFIX* pathogenic variant (see Genotype-Phenotype Correlations) and may require more frequent monitoring or a lower index of suspicion for the development of seizures.

4. Such as vomiting/nausea, dizziness, and fainting

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

NFIX-related Malan syndrome (MALNS) is an autosomal dominant disorder typically caused by a *de novo* genetic alteration.

Risk to Family Members

Parents of a proband

- Almost all individuals diagnosed with MALNS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* genetic alternation (either a pathogenic variant in *NFIX* or a heterozygous deletion of 19p13.2 that includes *NFIX*).
- Rarely, individuals diagnosed with MALNS have the disorder as the result of a genetic alteration inherited from a mosaic parent. Families with sib recurrence due to parental gonadal (or somatic and gonadal) mosaicism have been reported [Priolo et al 2018, Hancarova et al 2019, Sihombing et al 2020, Langley et al 2022].
- If the proband appears to be the only affected family member (i.e., a simplex case), genetic testing capable of identifying the genetic alternation identified in the proband is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the genetic alteration 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* genetic alteration.
    - The proband inherited a genetic alteration from a parent with gonadal (or somatic and gonadal) mosaicism [Priolo et al 2018, Hancarova et al 2019, Sihombing et al 2020, Langley et al 2022]. 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 (gonadal) cells only.

      * A parent with somatic and gonadal mosaicism for an *NFIX* pathogenic variant or 19p13.2 deletion may be mildly/minimally affected. Parental somatic and gonadal mosaicism has been reported in one family to date [Priolo et al 2018]. Presumed parental gonadal mosaicism was described in all other reported families with sib recurrence [Hancarova et al 2019, Sihombing et al 2020, Langley et al 2022].

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 affected and/or is known to have the *NFIX* pathogenic variant or 19p13.2 deletion identified in the proband, the risk to the sibs of inheriting the genetic alteration is 50%.
- If the genetic alteration identified in the proband cannot be detected in the leukocyte DNA of either parent and – if the proband has a deletion – neither parent has a balanced chromosome rearrangement involving the 19p13.2 region, the recurrence risk to sibs is slightly greater than that of the general

population because of the possibility of parental gonadal mosaicism [Priolo et al 2018, Hancarova et al 2019, Sihombing et al 2020, Langley et al 2022].

Offspring of a proband. Each child of an individual with MALNS has a 50% chance of inheriting the MALNS-related genetic alteration; however, reproductive fitness in MALNS is extremely low due to severe intellectual disability and, to date, individuals with MALNS are not known to reproduce.

Other family members. Given that all probands with MALNS reported to date have the disorder as the result of an *NFIX* pathogenic variant or 19p13.2 deletion that occurred *de novo* in the proband or in a mosaic parent, 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 young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the MALNS-related genetic alternation 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **Malan Syndrome Foundation**
  Email: info@malansyndrome.org
  malansyndrome.org
- **Organizzazione ASSI Gulliver APS**
  Italy
  Phone: 39 3403383967
  Email: info@assigulliver.it
  www.assigulliver.it
- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: info@childgrowthfoundation.org
  childgrowthfoundation.org
- **CoRDS Registry**
  Sanford Research

Phone: 605-312-6300
CoRDS Registry

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. NFIX-Related Malan Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NFIX	19p13.13	Nuclear factor 1 X-type	NFIX @ LOVD	NFIX	NFIX

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 NFIX-Related Malan Syndrome (View All in OMIM)

164005	NUCLEAR FACTOR I/X; NFIX
614753	MALAN SYNDROME; MALNS

Molecular Pathogenesis

Nuclear factor 1 X-type (NFIX) belongs to the nuclear factor 1 (NFI) family of transcription factors. Members of this family act as homodimers and heterodimers and bind with high affinity to the palindromic consensus sequence TTGGC(N5)GCCAA. In vertebrates, the *Nfi* gene family consists of four closely related genes (*Nfia*, *Nfib*, *Nfic*, and *Nfix*).They encode proteins with a conserved N-terminal DNA binding and dimerization domain and a C-terminal transactivation/repression domain. Almost all the pathogenic variants in *NFIX* are located in the DNA binding and dimerization domain, with few exceptions. Most pathogenic variants are nonsense, frameshift, and splice site pathogenic variants predicting premature stop codons, mostly in the 5' part of the mRNA. These pathogenic variants likely activate nonsense-mediated decay (NMD) of the respective mutated mRNA, thereby leading to haploinsufficiency. Conversely, all other observed missense pathogenic variants affect highly conserved residues within the DNA binding and dimerization domain that are expected to be crucial for protein function. A number of *NFIX* pathogenic missense variants involving positively charged amino acids (at positions Lys113, Arg115, Arg116, Arg121, Lys125, and Arg128) are clustered in a small region of 15 residues that is crucial for protein activity. The replacement of these positively charged residues by negatively charged residues suggest abnormal DNA binding.

NFIX pathogenic variants that cause *NFIX*-related Malan syndrome (MALNS) are typically located in exons coding for the DNA binding and dimerization domain (exons 2 to 5), with few exceptions. Some affected individuals have pathogenic variants located at the 3' end of the gene (in exons 6, 7, and 8). Their phenotypes do not differ in any way from the phenotype in other individuals with MALNS.

Mechanism of disease causation. Loss of function

Chapter Notes

Acknowledgments

The author gratefully acknowledges the patients, their families, and the support associations that have generously participated in the research described and referenced here. The author would also like to thank the clinician collaborator teams of physicians, genetic counselors, nurses, therapists, and trainees who have generously cared for these patients and contributed to produce guidelines for diagnosis and management of individuals with *NFIX*-related Malan syndrome (MALNS).

Revision History

- 1 August 2024 (ma) Review posted live
- 17 February 2023 (mp) Original submission

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