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Microphthalmia with Linear Skin Defects Syndrome

Synonyms: Microphthalmia, Dermal Aplasia, and Sclerocornea (MIDAS) Syndrome; MLS Syndrome

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Summary

Clinical characteristics

Microphthalmia with linear skin defects (MLS) syndrome is characterized by unilateral or bilateral microphthalmia and/or anophthalmia and linear skin defects, usually involving the face and neck, which are present at birth and heal with age, leaving minimal residual scarring. Other findings can include a wide variety of other ocular abnormalities (e.g., corneal anomalies, orbital cysts, cataracts), central nervous system involvement (e.g., structural anomalies, developmental delay, infantile seizures), cardiac concerns (e.g., hypertrophic or oncocytic cardiomyopathy, atrial or ventricular septal defects, arrhythmias), short stature, diaphragmatic hernia, nail dystrophy, hearing impairment, and genitourinary malformations. Inter- and intrafamilial variability is described.

Diagnosis/testing

The clinical diagnosis is established when the two major criteria (microphthalmia and/or anophthalmia *and* linear skin defects) are present and confirmed by identification of a pathogenic variant in *COX7B*, *HCCS*, or *NDUFB11*. However, persons with a molecular diagnosis of MLS syndrome in whom only one of the two major criteria was present have been reported: some show characteristic skin defects without ocular abnormalities and others show eye abnormalities without skin defects.

Management

Treatment of manifestations: Use of a prosthesis under the guidance of an oculoplastics specialist for severe microphthalmia and anophthalmia; routine dermatologic care for significant skin lesions; treatment of seizures and/or other neurologic abnormalities by a pediatric neurologist; appropriate developmental therapies and special education as indicated for developmental delay and intellectual disability; routine care for other medical concerns when present.

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Surveillance: Monitoring and follow up with ophthalmologist, dermatologist, pediatric neurologist, cardiologist, and other professionals as needed.

Genetic counseling

MLS syndrome is inherited in an X-linked manner and is generally lethal in males. Most cases are simplex (i.e., a single occurrence in a family), but rare familial occurrences have been described. Women who are affected or have an MLS syndrome-associated pathogenic variant have a 50% chance of passing the genetic alteration to each offspring. Because male conceptuses with an MLS syndrome-associated pathogenic variant are typically nonviable, the likelihood of a live-born affected child is less than 50%. Molecular genetic testing of at-risk female relatives to determine their genetic status, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for MLS syndrome are possible if the disease-causing genetic alteration has been identified in an affected family member.

Diagnosis

Suggestive Findings

Microphthalmia with linear skin defects (MLS) syndrome **should be suspected** in females with one or both major criteria especially in the presence of a family history consistent with X-linked inheritance with male lethality (see Figures 1, 2, and 3). Almost all individuals with MLS syndrome are female; however, a few affected males, typically with an XX karyotype, have been reported.

Major Criteria

- Microphthalmia and/or anophthalmia
  - Reported in 81% of affected individuals
  - Can be unilateral or bilateral (see Figure 2)
- Linear skin defects
  - Reported in 75% of affected individuals
  - Present at birth
  - Usually involve the face and neck (see Figure 3), although the scalp and occasionally the upper trunk may be involved [Zvulunov et al 1998]
  - Heal with age, leaving minimal residual scarring

Establishing the Diagnosis

The clinical signs observed in MLS syndrome are considered major if they are present in at least 70% of affected individuals and minor if they are less frequent (see Clinical Description, Minor Criteria).

The clinical diagnosis of MLS syndrome can be made when the two major criteria are present [al-Gazali et al 1990, Happle et al 1993]; however, persons with a molecular diagnosis of MLS syndrome in whom only one of the two major criteria was present have been reported: some show characteristic skin defects without ocular abnormalities (see Figure 1); others show eye abnormalities without skin defects [Morleo & Franco 2008].

Minor criteria in the presence of a family history consistent with X-linked inheritance with male lethality supports the clinical diagnosis of MLS syndrome.

Female proband. The diagnosis of MLS syndrome **is established** in a female proband by identification of a heterozygous pathogenic variant in *COX7B*, *HCCS*, or *NDUFB11* on molecular genetic testing (see Table 1).

Male proband. The diagnosis of MLS syndrome **is established** in a male proband by identification of a hemizygous pathogenic variant in *COX7B*, *HCCS*, or *NDUFB11* on molecular genetic testing (see Table 1).

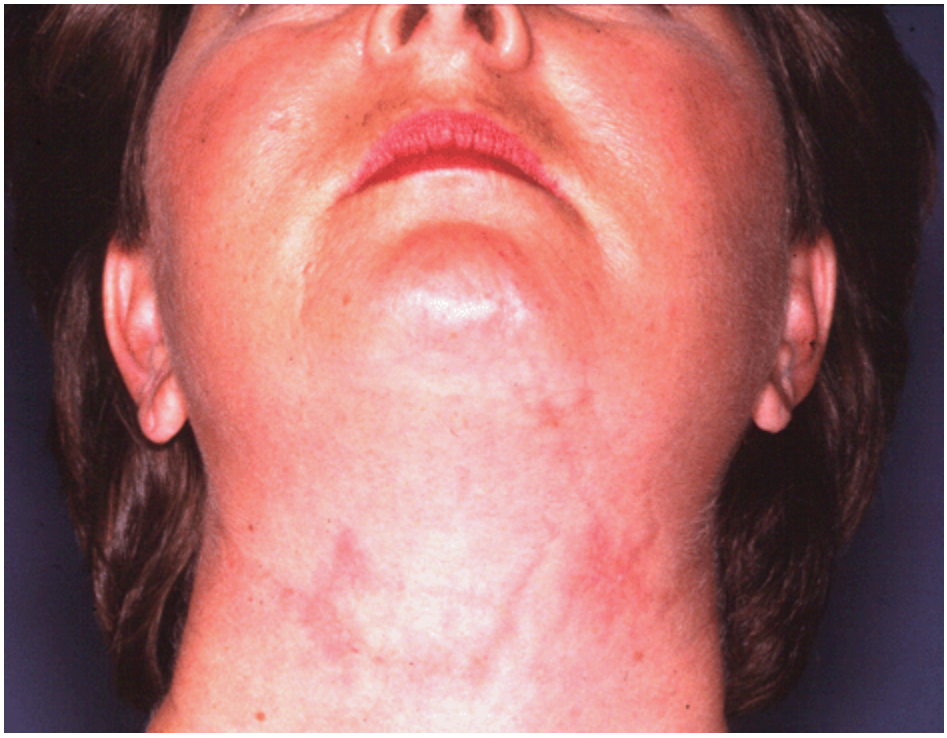

Figure 1. Reticulolinear scar lesions on the neck of a female age 36 years with an otherwise normal phenotype. Cytogenetic analysis revealed 46,X,del(X)(p22.3 pter) [Lindsay et al 1994].

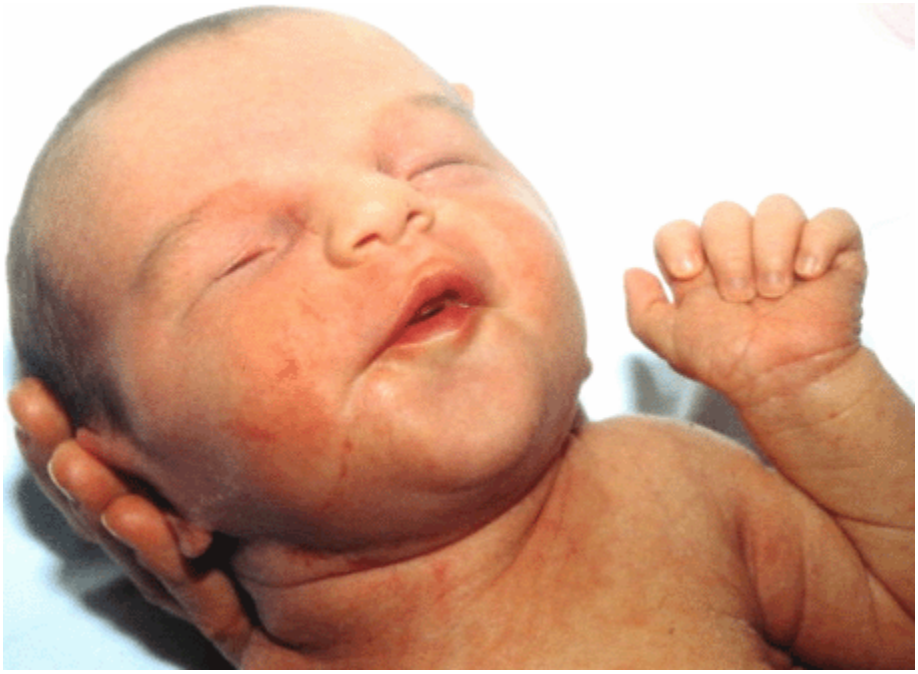

Figure 2. Bilateral microphthalmia and irregular linear skin areas involving the face and neck in a female infant with MLS syndrome who has a single-nucleotide variant in exon 6 of *HCCS* [Wimplinger et al 2006]

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

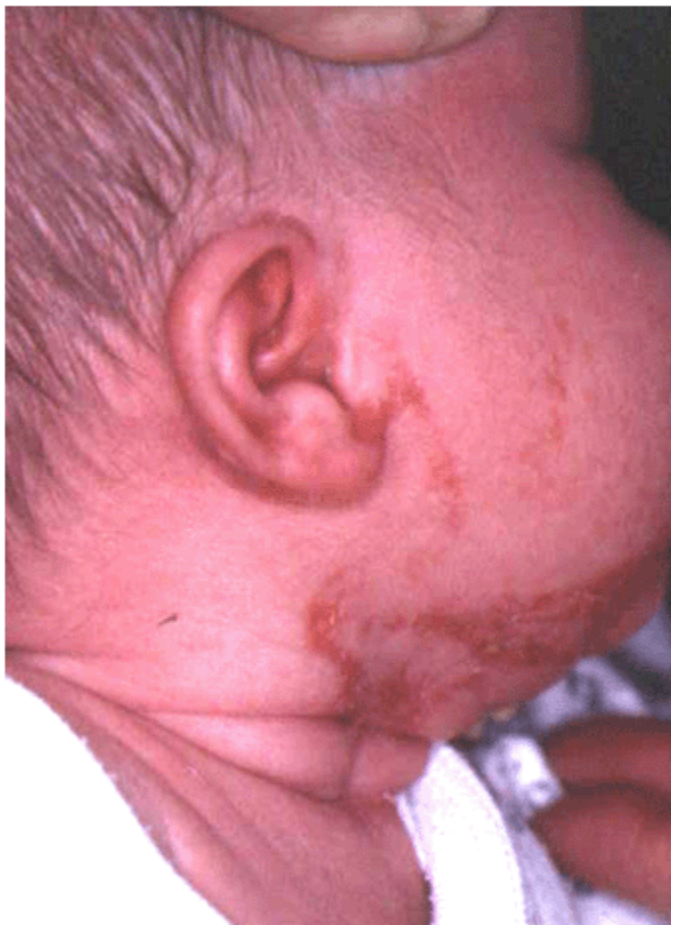

Figure 3. Typical linear skin lesions on the face and neck of a newborn female with MLS syndrome who has a deletion of exons 1-3 of *HCCS* [Morleo et al 2005, Wimplinger et al 2006]

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of MLS syndrome is broad, individuals with both major criteria are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of MLS syndrome has not been considered due to atypical findings are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of MLS syndrome, molecular genetic testing approaches can include chromosome microarray analysis or use of a multigene panel:

- **Chromosomal microarray analysis (CMA).** CMA should be the first genetic test as about 90% of MLS syndrome is caused by large copy number variants (CNVs), which cannot be detected by sequence analysis of *HCCS*.

  Note: (1) Deletions reported in the literature were most frequently detected by karyotype and FISH analysis; however, CMA is used more frequently than karyotyping in clinical practice for individuals with complex medical issues and has greater resolution and precision than a karyotype. Some complex karyotypes have been reported (e.g., 45,X[18]/46,X,der(X)(p22q21)[24]/46,X,del(X)(p22)[58] and 46,X,der(X)t(X;Y)); therefore, karyotype and/or FISH follow up may be necessary based on CMA results. (2) Apparently balanced translocations have been reported in affected individuals [Vergult et al 2013]. In

an affected person in whom other testing does not reveal a causative variant, karyotype analysis may be considered.

- **A multigene panel** that includes *COX7B*, *HCCS*, *NDUFB11*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition (if CMA is not diagnostic) 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of MLS syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is often performed. MLS syndrome is likely to be diagnosed by chromosome microarray (CMA), which is the best first test when multiple congenital abnormalities are present. If CMA is not diagnostic, additional genomic testing is indicated. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if CMA and exome sequencing are non-diagnostic.

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

Note: Although not used for diagnosis, X-chromosome inactivation studies have been performed in females with MLS syndrome. Skewed X-chromosome inactivation has been detected in 21 of the 22 individuals with MLS syndrome analyzed to date [Anguiano et al 2003, Wimplinger et al 2006, Cain et al 2007, Schluth et al 2007, Wimplinger et al 2007a, Wimplinger et al 2007b, Hobson et al 2009, Steichen-Gersdorf et al 2010, Alberry et al 2011]. In all individuals the abnormal X is inactive.

Table 1. Molecular Genetic Testing Used in MLS Syndrome

Gene [1, 2]	Proportion of MLS Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method		
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]	CMA [6, 7, 8]
COX7B	~5% [9]	3/3 [10]	Unknown [11]	NA
HCCS	~92% [9]	~8% [12]	See footnote 13.	~92% [14, 15]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of MLS Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method		
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]	CMA [6, 7, 8]
NDUFB11	~3% [9]	2/2 [9]	Unknown [11]	NA

NA = not applicable
1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. ClinGen: ISCA-20454. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium)
7. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the Xp22.3 region.
8. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
9. van Rahden et al [2015]
10. Indrieri et al [2012]
11. No data on detection rate of gene-targeted deletion/duplication analysis are available.
12. Vergult et al [2013], van Rahden et al [2014]
13. All large deletions reported to date are large deletions that encompass *HCCS* and surrounding sequence. Gene-targeted methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected. Thus, the detection rate for *HCCS*-targeted deletion assays would be ~92%; however, the deletion may not be fully characterized.
14. Vergult et al [2013], van Rahden et al [2014]
15. Note: Deletions reported in the literature were most frequently detected by karyotype and FISH analysis; however, CMA is more commonly used than karyotyping in clinical practice for individuals with complex medical issues and has greater resolution and precision than a karyotype. Some complex karyotypes have been reported (e.g., 45,X[18]/46,X,der(X)(p22q21)[24]/46,X,del(X)(p22)[58] and 46,X,der(X)t(X;Y)), therefore, karyotype and/or FISH follow up may be necessary based on CMA results.

Clinical Characteristics

Clinical Description

Microphthalmia with linear skin defects (MLS) syndrome is characterized by unilateral or bilateral microphthalmia or anophthalmia (see Figure 2) and/or jagged skin defects on the face and neck (see Figure 3). MLS syndrome is usually lethal in males [Kono et al 1999, Kherbaoui-Redouani et al 2003, Wimplinger et al 2006, Wimplinger et al 2007a, Wimplinger et al 2007b, Kapur et al 2008, Sharma et al 2008, Hobson et al 2009, Steichen-Gersdorf et al 2010, Alberry et al 2011].

Phenotypic variability. Inter- and intrafamilial phenotypic variability has been described. The manifestations differ among affected individuals and, although most display the classic phenotype of MLS syndrome, many have only a subset of characteristic features: some show the characteristic skin defects without ocular abnormalities, whereas others have eye abnormalities without skin defects [Morleo & Franco 2008]. For example, a female with a normal phenotype except for typical MLS syndrome skin defects (see Figure 1) had an affected female fetus with anencephaly.

Major Criteria

Eye findings. Microphthalmia and/or anophthalmia, when present, are evident at birth in 81% of affected individuals (Figure 2). Both microphthalmia and anophthalmia can be unilateral or bilateral.

Skin manifestations. In general, no new lesions are observed after birth and the skin defects heal variably with age, leaving minimal residual scarring. The cutaneous findings typically follow the lines of Blaschko corresponding to cell migration pathways evident during embryonic and fetal skin development, which (unlike dermatomes) do not correspond to innervation patterns. The restriction to the head and neck is thought to result from involvement of neural crest cells [al-Gazali et al 1990, Lindsay et al 1994].

Histologic skin findings. Happle et al [1993] coined the acronym MIDAS (for *mi*crophthalmia, *d*ermal *a*plasia, and *s*clerocornea), and argued that (in contrast to focal dermal hypoplasia) the erythematous lesions of dermal aplasia do not show herniation of fatty tissue. Subsequent histologic examination of skin biopsies of the linear, reticulated skin defects in six reported individuals yielded varied results, all confirming that dermal aplasia is not a histologic feature of MLS syndrome [Bird et al 1994, Eng et al 1994, Paulger et al 1997, Stratton et al 1998, Zvulunov et al 1998, Enright et al 2003].

Minor Criteria (in <70% of affected individuals)

Note: Categories are in descending order of frequency.

Other ocular abnormalities reported [Kobayashi et al 1998, Cape et al 2004, Wimplinger et al 2006, Kapur et al 2008, Carman et al 2009, García-Rabasco et al 2013, Vergult et al 2013, Herwig et al 2014, van Rahden et al 2014, van Rahden et al 2015]:

- Sclerocornea
- Orbital cysts
- Microcornea
- Eyelid fissures
- Corneal leukoma
- Iridocorneal adhesion (Peters anomaly)
- Congenital glaucoma with total/peripheral anterior synechiae
- Aniridia
- Cataracts
- A remnant of the anterior hyaloid artery
- Vitreous opacity
- Hypopigmented areas of the retinal pigment epithelium

Central nervous system involvement

- Agenesis of corpus callosum
- Anencephaly
- Microcephaly
- Hydrocephalus
- Developmental delay / intellectual disability
- Infantile seizures

Cardiac concerns

- Cardiomyopathy (hypertrophic or oncocytic)
- Atrial and ventricular septal defects
- Arrhythmias such as supraventricular tachycardia and ventricular fibrillation

Other reported findings (including frequency)

- Short stature (18/42)
- Genitourinary or lower intestinal malformations: bicornuate uterus, ambiguous genitalia, anterior or imperforate anus, penile hypospadias in rare males with a 46,XX karyotype (14/64)
- Hearing impairment (5/64)
- Nail dystrophy (3/55)
- Diaphragmatic hernia (3/64)
- Pseudotail [Alberry et al 2011]; as a single case report. This may be a coincidental finding and not typical of MLS syndrome.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed.

Nomenclature

MLS syndrome, first described by al-Gazali et al [1990], was initially known as Gazali-Temple syndrome.

MLS syndrome appears to be the most appropriate designation for this disorder.

Happle et al [1993] coined the acronym MIDAS (for *mi*crophthalmia, *d*ermal *a*plasia, and *s*clerocornea) for what is now known as MLS syndrome.

Prevalence

The disorder is rare; 64 individuals with a clinical diagnosis of MLS syndrome have been reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *COX7B* or *HCCS*.

NDUFB11 pathogenic variants have recently been associated with histiocytoid cardiomyopathy [Shehata et al 2015, Rea et al 2017] and sideroblastic anemia [Torraco et al 2017].

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of MLS Syndrome

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Focal dermal hypoplasia (Goltz syndrome)	*PORCN*	XL	• Distinctive skin findings (dermal hypoplasia) • Ophthalmologic manifestations	In focal dermal hypoplasia: limb & skeletal malformations
Incontinentia pigmenti (IP)	*IKBKG* (*NEMO*)	XL	• Skin lesions • Ocular abnormalities (present in 35% of those w/IP diagnosis)	In incontinentia pigmenti: • Erythema followed by blisters (vesicles) anywhere on the body • Verrucous lesions

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Oculocerebro-cutaneous syndrome (OCCS) (OMIM 164180)	?	?	• Focal skin defects • Anophthalmia / microphthalmia	In OCCS: • Observed in males prevalently [1] • Brain malformation [2] • Psychomotor impairment & episodes of seizures
Aicardi syndrome	?	XL	• Microphthalmia • Pigmentary lesions of the skin	In Aicardi syndrome: [3] • Agenesis of the corpus callosum • Distinctive chorioretinal lacunae • Infantile spasms

? = unknown; MOI = mode of inheritance; XL = X-linked

1. MLS syndrome is male lethal.

2. Polymicrogyria or periventricular heterotopia, agenesis of the corpus callosum, hypoplastic vermis of the cerebellum, hydrocephalus

3. Two of the three classic features (agenesis of the corpus callosum, distinctive chorioretinal lacunae, infantile spasms) are needed to make the diagnosis of Aicardi syndrome; these features are rarely found associated with microphthalmia in MLS syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with microphthalmia with linear skin lesions (MLS) syndrome, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Ophthalmologic examination
- Dermatologic evaluation for skin lesions
- Brain MRI for corpus callosum dysgenesis and other neurologic abnormalities
- Developmental assessment, with further evaluation if significant delays are identified
- Cardiac evaluation
- Hearing evaluation, as hearing loss is observed in 8% of cases
- Consideration of abdominal MRI and standard protocols for management of diaphragmatic hernia
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The following are appropriate:

- Under the guidance of an oculoplastics specialist, use of a prosthesis in severe microphthalmia and anophthalmia
- Regular care by a dermatologist for individuals with significant skin lesions
- Referral to a pediatric neurologist for evaluation and treatment if microcephaly, seizures, and/or other neurologic abnormalities are present
- Appropriate developmental therapies and special education as indicated for developmental delay and intellectual disability

- Standard care for cardiac concerns and other malformations, when present

Surveillance

Monitoring and follow up with ophthalmologist, dermatologist, pediatric neurologist, and other professionals as needed is appropriate.

Affected individuals with cardiac concerns should have regular complete evaluation at intervals determined by the cardiologist.

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

Microphthalmia with linear skin lesions (MLS) syndrome is inherited in an X-linked manner and is generally lethal in males.

Most affected individuals represent simplex cases (i.e., a single occurrence in a family).

Risk to Family Members

Parents of a female proband

- Most females with MLS syndrome have a *de novo* pathogenic variant.
- In rare cases, a female proband has inherited an MLS syndrome-related pathogenic variant from her mother, who may or may not be affected [Allanson & Richter 1991, Lindsay et al 1994, Mücke et al 1995, Wimplinger et al 2006, Wimplinger et al 2007a, Vergult et al 2013, Kluger et al 2014, van Rahden et al 2015]. Significant intrafamilial phenotypic variability has been observed.
- Detailed clinical evaluation of the mother and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant.
    - If the mother has clinical findings of MLS syndrome or if she has another affected relative, she is an obligate heterozygote for a pathogenic variant in *COX7B*, *HCCS*, or *NDUFB11*.
    - If a *COX7B*, *HCCS*, or *NDUFB11* pathogenic variant has been identified in the proband, molecular genetic testing of the mother is appropriate to more accurately assess recurrence risk to sibs.

Parents of a male proband

- Live-born affected males with MLS syndrome are rare and are the result of a new chromosomal aberration (46,XX karyotype and an X/Y translocation).
- Affected males who do not survive pregnancy may have inherited the pathogenic variant from their mothers or may have a *de novo* pathogenic variant.

Sibs of a proband. The risk to sibs depends on the genetic status of the mother.

- If the mother of a proband is affected and/or is known to have a *COX7B*, *HCCS*, or *NDUFB11* pathogenic variant, the chance of transmitting the pathogenic variant at conception is 50%. Because male conceptuses who inherit such a pathogenic variant are typically nonviable, the likelihood of a live-born affected child is less than 50%.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *COX7B*, *HCCS*, or *NDUFB11* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to the sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism.

Offspring of a female proband. Women with a *COX7B*, *HCCS*, or *NDUFB11* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

- Males who inherit the pathogenic variant will be affected, often with lethality during gestation.
- Females who inherit the pathogenic variant will be heterozygotes and will have a range of clinical manifestations (see Clinical Description).
- Note: If the proband is mosaic for a pathogenic variant, the risk to her offspring is as high as 50%, depending on the level of mosaicism in her germline.

Offspring of a male proband. Affected males are not known to reproduce.

Other family members. If the mother of the proband also has a pathogenic variant, her female family members may be at risk of having the pathogenic variant (and may or may not have clinical findings).

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous for this X-linked disorder will have a range of clinical manifestations (see Clinical Description). (2) Identification of female heterozygotes requires either (a) prior identification of the pathogenic variant in the family or (b) if an affected individual is not available for testing, molecular genetic testing as detailed in Establishing the Diagnosis.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or are heterozygotes or who are at increased risk of being heterozygotes or affected.

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

Prenatal Testing and Preimplantation Genetic Testing

Once a *COX7B*, *HCCS*, or *NDUFB11* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MLS syndrome are possible.

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.

- **International Children's Anophthalmia Network (ICAN)**
  Phone: 800-580-ican
  Email: info@anophthalmia.org
  www.anophthalmia.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org

Molecular Genetics

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

Table A. Microphthalmia with Linear Skin Defects Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COX7B	Xq21.1	Cytochrome c oxidase subunit 7B, mitochondrial		COX7B	COX7B
HCCS	Xp22.2	Holocytochrome c-type synthase	HCCS @ LOVD	HCCS	HCCS
NDUFB11	Xp11.3	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial		NDUFB11	NDUFB11

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 Microphthalmia with Linear Skin Defects Syndrome (View All in OMIM)

300056	HOLOCYTOCHROME C SYNTHASE; HCCS
300403	NADH-UBIQUINONE OXIDOREDUCTASE 1 BETA SUBCOMPLEX, 11; NDUFB11
300885	CYTOCHROME c OXIDASE, SUBUNIT 7B; COX7B

Table B. continued from previous page.

300887	LINEAR SKIN DEFECTS WITH MULTIPLE CONGENITAL ANOMALIES 2; LSDMCA2
300952	LINEAR SKIN DEFECTS WITH MULTIPLE CONGENITAL ANOMALIES 3; LSDMCA3
309801	LINEAR SKIN DEFECTS WITH MULTIPLE CONGENITAL ANOMALIES 1; LSDMCA1

Introduction

COX7B, *HCCS*, and *NDUFB11* encode proteins necessary for the proper functioning of the mitochondrial respiratory chain (MRC). "Canonic" mitochondrial diseases are usually characterized by postnatal organ failure rather than impaired development: in that regard microphthalmia with linear skin defects (MLS) syndrome can be defined as an unconventional mitochondrial disorder. A combined effect of mitochondrial respiration defects and enhanced cell death are hypothesized to result in the brain and eye abnormalities observed in MLS syndrome.

The three genes associated with MLS syndrome are all X-linked. Females with MLS syndrome show high inter- and intrafamilial phenotypic variability. Individuals can show the full MLS syndrome phenotype, or they can show isolated ocular manifestations, or aplastic skin areas restricted to face and neck with no additional abnormalities. Females with MLS syndrome may also show no features at all. A possible explanation for this clinical variability is the degree of skewed X chromosome inactivation observed in different tissues [Morleo & Franco 2008].

COX7B

Gene structure. *COX7B* (RefSeq: NM_001866.2) has three coding exons. The gene spans 5.9 kb, and its transcribed mRNA is 456 bp. No information is available on alternative splicing.

Pathogenic variants. The clinically relevant variants reported to date include p.Gln19Ter, c.196delC, and c.41-2A>G [Indrieri et al 2012] (see Table 3).

Table 3. *COX7B* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.55C>T	p.Gln19Ter	NM_001866.2 NP_001857.1
c.196delC	p.Leu66CysfsTer48	
c.41-2A>G	p.Val14GlyfsTer19	

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.

Normal gene product. *COX7B* is ubiquitously expressed and encodes an 80-amino-acid mitochondrial protein that has been shown to be an integral component of cytochrome *c* oxidase (COX), the mitochondrial respiratory chain (MRC) complex IV. COX7B subunit is necessary for COX activity, COX assembly, and mitochondrial respiration [Indrieri et al 2013].

Abnormal gene product. Microphthalmia with linear skin defects (MLS) syndrome is caused by pathogenic loss-of-function variants in *COX7B*, which promote severe impairment of the MRC's terminal segment [Indrieri et al 2012]. Moreover, downregulation of the *COX7B* homolog (*cox7B*) in medaka fish (*Oryzias latipes*) results in microcephaly and microphthalmia, thus indicating an essential role for complex IV activity and MRC function in vertebrate CNS development [Indrieri et al 2013].

HCCS

Gene structure. *HCCS* has seven exons, six of which are coding exons. The gene spans 11.8 kb, and its transcribed mRNA is long at 2,365 bp. No information on alternative splicing for this transcript is available (see Table 4). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The majority of *HCCS* disease-causing aberrations are large deletions involving the Xp22.2 chromosome region [Vergult et al 2013]; other reported pathogenic variants include p.Arg197Ter, p.Arg217Cys, and p.Glu159Lys, and a deletion of exons 1-3 [Wimplinger et al 2006, Wimplinger et al 2007b] (see Table 4).

Table 4. *HCCS* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.589C>T	p.Arg197Ter	NM_005333.4 NP_005324.3
c.649C>T	p.Arg217Cys	
c.475G>A	p.Glu159Lys	

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Normal gene product. *HCCS* is expressed in a wide variety of tissues and encodes a mitochondrial enzyme of 268 amino acids, the holocytochrome *c*-type synthase, which catalyzes the covalent attachment of heme to apocytochrome *c*, thereby leading to the mature form holocytochrome *c* [Bernard et al 2003].

The product of the HCCS-catalyzed reaction, cytochrome *c*, has two cellular functions: it is implicated in oxidative phosphorylation (OXPHOS), and it is released from mitochondria upon proapoptotic stimuli, thus playing an important role in caspase-dependent apoptosis [Jiang & Wang 2004].

Abnormal gene product. MLS syndrome is caused by pathogenic loss-of-function variants in *HCCS*. Recently it was hypothesized that deficiency of HCCS may not only cause functional deficits in OXPHOS, but may also lead to severe constraints in the process of apoptosis. Thus, loss of HCCS function may disturb the balance between necrosis and apoptosis and push cell death toward necrosis [Wimplinger et al 2006]. Necrosis bears the danger of inflammatory reactions, leading to substantial damage of neighboring cells that could be a key element in developing eye malformations as well as other MLS syndrome-specific features in affected individuals.

NDUFB11

Gene structure. *NDUFB11* spans 3 kb; its transcribed mRNA is 2,365 bp long. The gene comprises three exons; exon 2 is alternatively spliced [Petruzzella et al 2007].

Pathogenic variants. Reported pathogenic variants include p.Arg88Ter and c.402delG [van Rahden et al 2015].

Table 5. *NDUFB11* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.262C>T	p.Arg88Ter	NM_019056.6 NP_061929.2
c.402delG	p.Arg134SerfsTer3	

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.

Normal gene product. The protein encoded by *NDUFB11* is the 17.3-kd subunit 11 of the NADH dehydrogenase (ubiquinone) 1 beta subcomplex and is part of the MRC complex I (cI). The longer transcript encodes a 163-amino-acid (aa) protein, while the shorter one encodes a more abundant protein consisting of 153 aa. The NDUFB11 protein is indispensable for assembly of the cI membrane arm, for maturation of the cI holocomplex, and for cI-dependent mitochondrial respiration.

Abnormal gene product. MLS syndrome is caused by pathogenic loss-of-function variants in *NDUFB11*, resulting in defective cI assembly and activity leading to impairment of mitochondrial respiration [van Rahden et al 2015]. Moreover, reduced NDUFB11 is associated with slower cell growth and increased apoptosis [van Rahden et al 2015].

A combined effect of MRC defects and enhanced cell death has been shown to underlie the brain and eye abnormalities observed in an hccs-deficient medaka fish model [Indrieri et al 2013].

References

Literature Cited

Alberry MS, Juvanic G, Crolla J, Soothill P, Newbury-Ecob R. Pseudotail as a feature of microphthalmia with linear skin defects syndrome. Clin Dysmorphol. 2011;20:111–3. PubMed PMID: 21200317.

al-Gazali LI, Mueller RF, Caine A, Antoniou A, McCartney A, Fitchett M, Dennis NR. Two 46,XX,t(X;Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3. J Med Genet. 1990;27:59–63. PubMed PMID: 2308157.

Allanson J, Richter S. Linear skin defects and congenital microphthalmia: a new syndrome at Xp22.2. J Med Genet. 1991;28:143–4. PubMed PMID: 2002490.

Anguiano A, Yang X, Felix JK, Hoo JJ. Twin brothers with MIDAS syndrome and XX karyotype. Am J Med Genet A. 2003;119A:47–9. PubMed PMID: 12707958.

Bernard DG, Gabilly ST, Dujardin G, Merchant S, Hamel PP. Overlapping specificities of the mitochondrial cytochrome c and c1 heme lyases. J Biol Chem. 2003;278:49732–42. PubMed PMID: 14514677.

Bird LM, Krous HF, Eichenfield LF, Swalwell CI, Jones MC. Female infant with oncocytic cardiomyopathy and microphthalmia with linear skin defects (MLS): a clue to the pathogenesis of oncocytic cardiomyopathy? Am J Med Genet. 1994;53:141–8. PubMed PMID: 7856638.

Cain CC, Saul D, Attanasio L, Oehler E, Hamosh A, Blakemore K, Stetten G. Microphthalmia with linear skin defects (MLS) syndrome evaluated by prenatal karyotyping, FISH and array comparative genomic hybridization. Prenat Diagn. 2007;27:373–9. PubMed PMID: 17286317.

Cape CJ, Zaidman GW, Beck AD, Kaufman AH. Phenotypic variation in ophthalmic manifestations of MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea). Arch Ophthalmol. 2004;122:1070–4. PubMed PMID: 15249380.

Carman KB, Yakut A, Sabuncu I, Yarar C. MIDAS (microphthalmia, dermal aplasia, sclerocornea) syndrome with central nervous system abnormalities. Clin Dysmorphol. 2009;18:234–5. PubMed PMID: 19726975.

Eng A, Lebel RR, Elejalde BR, Anderson C, Bennett L. Linear facial skin defects associated with microphthalmia and other malformations, with chromosome deletion Xp22.1. J Am Acad Dermatol. 1994;31:680–2. PubMed PMID: 8089303.

Enright F, Campbell P, Stallings RL, Hall K, Green AJ, Sweeney E, Barnes L, Watson R. Xp22.3 microdeletion in a 19-year-old girl with clinical features of MLS syndrome. Pediatr Dermatol. 2003;20:153–7. PubMed PMID: 12657015.

García-Rabasco A, De-Unamuno B, Martínez F, Febrer-Bosch I, Alegre-de-Miquel V. Microphtalmia with linear skin defects syndrome. Pediatr Dermatol. 2013;30:e230–31. PubMed PMID: 22612277.

Happle R, Daniëls O, Koopman RJ. MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea): an X-linked phenotype distinct from Goltz syndrome. Am J Med Genet. 1993;47:710–3. PubMed PMID: 8267001.

Herwig MC, Loeffler KU, Gembruch U, Kuchelmeister K, Müller AM. Anterior Segment Developmental Anomalies in a 33-Week-Old Fetus with MIDAS Syndrome. Pediatr Dev Pathol. 2014;17:491–5. PubMed PMID: 25291437.

Hobson GM, Gibson CW, Aragon M, Yuan ZA, Davis-Williams A, Banser L, Kirkham J, Brook AH. A large X-chromosomal deletion is associated with microphthalmia with linear skin defects (MLS) and amelogenesis imperfecta (XAI). Am J Med Genet A. 2009;149A:1698–705. PubMed PMID: 19610109.

Indrieri A, van Rahden VA, Tiranti V, Morleo M, Iaconis D, Tammaro R, D'Amato I, Conte I, Maystadt I, Demuth S, Zvulunov A, Kutsche K, Zeviani M, Franco B. Mutations in COX7B cause microphthalmia with linear skin lesions, an unconventional mitochondrial disease. Am J Hum Genet. 2012;91:942–49. PubMed PMID: 23122588.

Indrieri A, Conte I, Chesi G, Romano A, Quartararo J, Tate R, Ghezzi D, Zeviani M, Goffrini P, Ferrero I, Bovolenta P, Franco B. The impairment of HCCS leads to MLS syndrome by activating a non-canonical cell death pathway in the brain and eyes. EMBO Mol Med. 2013;5:280–93. PubMed PMID: 23239471.

Jiang X, Wang X. Cytochrome C-mediated apoptosis. Annu Rev Biochem. 2004;73:87–106. PubMed PMID: 15189137.

Kapur R, Tu EY, Toyran S, Shah P, Vangveeravong S, Lloyd WC 3rd, Edward DP. Corneal pathology in microphthalmia with linear skin defects syndrome. Cornea. 2008;27:734–8. PubMed PMID: 18580270.

Kherbaoui-Redouani L, Eschard C, Bednarek N, Morville P, Bednare N. Cutaneous aplasia, non compaction of the left ventricle and severe cardiac arrhythmia: a new case of MLS syndrome (microphtalmia with linear skin defects). Arch Pediatr. 2003;10:224–6. PubMed PMID: 12829336.

Kluger N, Bouissou A, Tauzin L, Puechberty J, Dereure O. Congenital linear streaks on the face and neck and microphthalmia in an infant girl. Acta Derm Venereol. 2014;94:342–3. PubMed PMID: 24096629.

Kobayashi M, Kiyosawa M, Toyoura T, Tokoro T. An XX male with microphthalmos and sclerocornea. J Pediatr Ophthalmol Strabismus. 1998;35:122–4. PubMed PMID: 9559515.

Kono T, Migita T, Koyama S, Seki I. Another observation of microphthalmia in an XX male: microphthalmia with linear skin defects syndrome without linear skin lesions. J Hum Genet. 1999;44:63–8. PubMed PMID: 9929982.

Lindsay EA, Grillo A, Ferrero GB, Roth EJ, Magenis E, Grompe M, Hultén M, Gould C, Baldini A, Zoghbi HY, Ballabio A. Microphthalmia with linear skin defects (MLS) syndrome: clinical, cytogenetic and molecular characterization. Am J Med Genet. 1994;49:229–34. PubMed PMID: 8116674.

Morleo M, Franco B. Dosage compensation of the mammalian X chromosome influences the phenotypic variability of X-linked dominant male-lethal disorders. J Med Genet. 2008;45:401–8. PubMed PMID: 18463129.

Morleo M, Pramparo T, Perone L, Gregato G, Le Caignec C, Mueller RF, Ogata T, Raas-Rothschild A, de Blois MC, Wilson LC, Zaidman G, Zuffardi O, Ballabio A, Franco B. Microphthalmia with linear skin defects (MLS) syndrome: clinical, cytogenetic, and molecular characterization of 11 cases. Am J Med Genet A. 2005;137:190–8. PubMed PMID: 16059943.

Mücke J, Hoepffner W, Thamm B, Theile H. MIDAS syndrome (microphthalmia, dermal aplasia and sclerocornea): an autonomous entity with linear skin defects within the spectrum of focal hypoplasias. Eur J Dermatol. 1995;5:197–203.

Paulger BR, Kraus EW, Pulitzer DR, Moore CM. Xp microdeletion syndrome characterized by pathognomonic linear skin defects on the head and neck. Pediatr Dermatol. 1997;14:26–30. PubMed PMID: 9050760.

Petruzzella V, Tessa A, Torraco A, Fattori F, Dotti MT, Bruno C, Cardaioli E, Papa S, Federico A, Santorelli FM. The NDUFB11 gene is not a modifier in Leber hereditary optic neuropathy. Biochem Biophys Res Commun. 2007;355:181–7. PubMed PMID: 17292333.

Rea G, Homfray T, Till J, Roses-Noguer F, Buchan RJ, Wilkinson S, Wilk A, Walsh R, John S, McKee S, Stewart FJ, Murday V, Taylor RW, Ashworth M, Baksi AJ, Daubeney P, Prasad S, Barton PJR, Cook SA, Ware JS. Histiocytoid cardiomyopathy and microphthalmia with linear skin defects syndrome: phenotypes linked by truncating variants in *NDUFB11*. Cold Spring Harb Mol Case Stud. 2017;3:a001271. PubMed PMID: 28050600.

Schluth C, Cossee M, Girard-Lemaire F, Carelle N, Dollfus H, Jeandidier E, Flori E. Phenotype in X chromosome rearrangements: pitfalls of X inactivation study. Pathol Biol (Paris). 2007;55:29–36. PubMed PMID: 16690229.

Sharma VM, Ruiz de Luzuriaga AM, Waggoner D, Greenwald M, Stein SL. Microphthalmia with linear skin defects: a case report and review. Pediatr Dermatol. 2008;25:548–52. PubMed PMID: 18950397.

Shehata BM, Cundiff CA, Lee K, Sabharwal A, Lalwani MK, Davis AK, Agrawal V, Sivasubbu S, Iannucci GJ, Gibson G. Exome sequencing of patients with histiocytoid cardiomyopathy reveals a de novo NDUFB11 mutation that plays a role in the pathogenesis of histiocytoid cardiomyopathy. Am J Med Genet A. 2015;167A:2114–21. PubMed PMID: 25921236.

Steichen-Gersdorf E, Griesmaier E, Pientka FK, Kotzot D, Kutsche K. A severe form of the X-linked microphthalmia with linear skin defects syndrome in a female newborn. Clin Dysmorphol. 2010;19:82–4. PubMed PMID: 20179582.

Stratton RF, Walter CA, Paulgar BR, Price ME, Moore CM. Second 46,XX males with MLS syndrome. Am J Med Genet. 1998;76:37–41. PubMed PMID: 9508062.

Torraco A, Bianchi M, Verrigni D, Gelmetti V, Riley L, Niceta M, Martinelli D, Montanari A, Guo Y, Rizza T, Diodato D, Di Nottia M, Lucarelli B, Sorrentino F, Piemonte F, Francisci S, Tartaglia M, Valente EM, Dionisi-Vici C, Christodoulou J, Bertini E, Carrozzo R. A novel mutation in NDUFB11 unveils a new clinical phenotype associated with lactic acidosis and sideroblastic anemia. Clin Genet. 2017;91:441–47. PubMed PMID: 27102574.

van Rahden VA, Rau I, Fuchs S, Kosyna FK, Larangeira de Almeida H Jr, Fryssira F, Isidor B, Jauch A, Joubert M, Lachmeijer AMA, Zweier C, Moog U, Kutsche K. Clinical spectrum of females with HCCS mutation: from no clinical signs to a neonatal lethal form of the microphthalmia with linear skin defects (MLS) syndrome. Orphanet J Rare Dis. 2014;9:53. PubMed PMID: 24735900.

van Rahden VA, Fernandez-Vizarra E, Alawi M, Brand K, Florence Fellmann F, Horn D, Massimo Zeviani Z, Kutsche K. Mutations in NDUFB11, Encoding a complex I component of the mitochondrial respiratory chain, cause microphthalmia with linear skin defects syndrome. Am J Hum Genet. 2015;96:640–50. PubMed PMID: 25772934.

Vergult S, Leroy B, Claerhout I, Menten B. Familial cases of a submicroscopic Xp22.2 deletion: genotype-phenotype correlation in microphthalmia with linear skin defects syndrome. Mol Vis. 2013;19:311–8. PubMed PMID: 23401659.

Wimplinger I, Morleo M, Rosenberger G, Iaconis D, Orth U, Meinecke P, Lerer I, Ballabio A, Gal A, Franco B, Kutsche K. Mutations of the mitochondrial holocytochrome c-type synthase in X-linked dominant microphthalmia with linear skin defects syndrome. Am J Hum Genet. 2006;79:878–89. PubMed PMID: 17033964.

Wimplinger I, Rauch A, Orth U, Schwarzer U, Trautmann U, Kutsche K. Mother and daughter with a terminal Xp deletion: implication of chromosomal mosaicism and X-inactivation in the high clinical variability of the

microphthalmia with linear skin defects (MLS) syndrome. Eur J Med Genet. 2007a;50:421–31. PubMed PMID: 17845869.

Wimplinger I, Shaw GM, Kutsche K. HCCS loss-of-function missense mutation in a female with bilateral microphthalmia and sclerocornea: a novel gene for severe ocular malformations? Mol Vis. 2007b;13:1475–82. PubMed PMID: 17893649.

Zvulunov A, Kachko L, Manor E, Shinwell E, Carmi R. Reticulolinear aplasia cutis congenita of the face and neck: a distinctiv cutaneous manifestation in several syndromes linked to Xp22. Br J Dermatol. 1998;138:1046–52. PubMed PMID: 9747372.

Chapter Notes

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