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LPIN2-Related Majeed Syndrome

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Summary

Clinical characteristics

Individuals with *LPIN2*-related Majeed syndrome typically experience multisystem inflammatory symptoms, including chronic sterile multifocal osteomyelitis, recurrent bone pain, recurrent fever, failure to thrive, dyserythropoietic anemia, and neutrophilic dermatosis. Recurrent bone pain is frequently localized near the joints, often of the long bones of the lower extremities. Recurrent osteomyelitis with joint swelling can lead to subsequent joint contractures. Congenital dyserythropoietic, microcytic anemia can range from mild to severe and sometimes requires blood transfusion. Neutrophilic dermatosis typically presents as transient painful erythematous plaques, pustules, or nodules with neutrophilic infiltrates. Other features of *LPIN2*-related Majeed syndrome include the development of hepatosplenomegaly and gastrointestinal symptoms, such as recurrent abdominal pain and/or recurrent diarrhea. As more families are being described, individuals with milder features are now being recognized.

Diagnosis/testing

The diagnosis of *LPIN2*-related Majeed syndrome is established in a proband with suggestive findings and biallelic pathogenic variants in *LPIN2* identified by molecular genetic testing.

Management

Treatment of manifestations: Anti-inflammatory treatment decreases inflammation and reduces flare-ups. Anti-inflammatory drugs can include anti-interleukin-1 (anti-IL-1) therapy (anakinra 1.5 mg/kg/day with titration as needed or canakinumab 2 mg/kg every 4 or 8 weeks), nonsteroidal anti-inflammatory drugs, corticosteroids, or methotrexate. While one of the anti-IL-1 therapies is the drug of choice, these drugs may not be universally available. Severe anemia may require blood transfusion. Physical therapy and/or occupational therapy can help motor delays and joint contractures.

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Surveillance: Measurement of inflammatory markers (ESR, CRP) and growth parameters, assessment of range of motion of joints, and physical examination to assess for hepatosplenomegaly and dermatosis at each visit. Complete blood count (CBC) with differential to assess for anemia and neutropenia every six months. Abdominal ultrasound as clinically indicated to monitor those with hepatosplenomegaly.

Agents/circumstances to avoid: For affected individuals managed with biologic or immunosuppressive medications, live-attenuated vaccines should be avoided, when possible.

Evaluations of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual to identify as early as possible those who would benefit from prompt initiation of anti-inflammatory treatment. Evaluations can include targeted molecular genetic testing (if the pathogenic variants in the family are known) or clinical assessment (history and physical exam for signs/symptoms of systemic inflammation, full skin examination for rashes, assessment of inflammatory markers [serum CRP and ESR], and CBC with differential) if the pathogenic variants in the family are not known.

Pregnancy management: There is limited data on the safety of anakinra or canakinumab during human pregnancy, although no pattern of anomalies in exposed fetuses has been reported. The use of corticosteroids during human pregnancy has been associated with an increased risk of cleft lip with or without cleft palate. Methotrexate should be avoided in pregnancy, as it is known to be harmful to the developing fetus and can lead to pregnancy loss and/or birth defects.

Genetic counseling

LPIN2-related Majeed syndrome is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *LPIN2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *LPIN2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *LPIN2*-related Majeed syndrome have been published.

Suggestive Findings

LPIN2-related Majeed syndrome **should be suspected** in individuals with the following clinical, supportive laboratory, imaging, and family history findings.

Clinical findings

- Recurrent bone pain near the joints, often of the long bones of the lower extremities
- Joint swelling and subsequent joint contracture
- Chronic recurrent multifocal osteomyelitis that is sterile
- Neutrophilic dermatosis, which may present as painful erythematous plaques, pustules, or nodules with neutrophilic infiltrates

  Note: This finding can be transient.
- Failure to thrive
- Recurrent fever

- Hepatosplenomegaly
- Gastrointestinal issues, including recurrent abdominal pain and/or recurrent diarrhea

Supportive laboratory findings

- Elevated erythrocyte sedimentation rate (ESR), typically above 100 mm/hr, and C-reactive protein (CRP), often above 50 mg/L
- Neutropenia
- Congenital dyserythropoietic, microcytic anemia, ranging from mild to severe, that sometimes requires blood transfusion
- Bone marrow biopsy that demonstrates erythroid hyperplasia with binuclearity or multinuclearity suggestive of congenital dyserythropeitic anemia

  Note: Bone marrow biopsy is not required to make this diagnosis

Imaging findings. Radiographic evidence of chronic nonbacterial osteomyelitis

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *LPIN2*-related Majeed syndrome **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *LPIN2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *LPIN2* variants of uncertain significance (or of one known *LPIN2* pathogenic variant and one *LPIN2* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with periodic fevers and/or autoinflammatory 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 *LPIN2*-related Majeed syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *LPIN2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A monogenic autoinflammatory disease multigene panel** or **monogenic inborn errors of human immunity disease panel** that includes *LPIN2* 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 list of genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and is 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 periodic fevers and/or autoinflammatory findings, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *LPIN2*-Related Majeed Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
LPIN2	Sequence analysis [3]	18/19 families (94.7%) [4]
	Gene-targeted deletion/duplication analysis [5]	1/19 (5.2%) [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the authors' observations and the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Individuals with *LPIN2*-related Majeed syndrome typically experience multisystem inflammatory symptoms, including chronic multifocal osteomyelitis, recurrent bone pain, recurrent fever, failure to thrive, dyserythropoietic anemia, and neutrophilic dermatosis. Because more than half of affected individuals have recurrent fever as one of the first manifestations, *LPIN2*-related Majeed syndrome should be considered in the spectrum of periodic fever syndromes in children (see Differential Diagnosis). As more families are being described, individuals with milder features are now being recognized.

To date, 32 individuals from 19 families have been identified with a pathogenic variant in *LPIN2* [Chavan et al 2021; Ferguson & El-Shanti 2021; Authors, personal observation]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *LPIN2*-Related Majeed Syndrome: Frequency of Select Features

Feature	# of Persons w/Feature	Comment
Chronic multifocal osteomyelitis	32/32 (100%)	Recurrent episodes
Recurrent bone pain	32/32 (100%)	
Microcytic anemia	29/30 (97%)	
Recurrent fever	17/32 (53%)	
Growth restriction / failure to thrive	12/25 (48%)	
Hepatosplenomegaly	10/22 (45%)	
Dermatosis	4/28 (14%)	

Chronic recurrent multifocal osteomyelitis (CRMO). Almost all affected individuals present with recurrent bone pain or clinical or radiologic evidence of CRMO. The symptoms usually start in the first two years of life. The bone pain is usually localized in and around major joints in the long bones, especially in the lower limbs. Clinical examination may reveal local swelling, redness, or warmth of the affected bone or joint. Biopsy performed in some affected individuals reveals sterile osteomyelitis [Ferguson & El-Shanti 2021]. Due to recurrent osteomyelitis, some individuals may develop joint contractures, which may be severe enough to affect their daily living activities [Chavan et al 2021].

Hematologic findings. Affected individuals can have microcytic hypochromic anemia and sometimes may require blood transfusion. Bone marrow cytology may show abnormalities like erythroid hyperplasia and multinuclear cells suggestive of congenital dyserythropoietic anemia. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated in all affected individuals (see Suggestive Findings). Neutropenia has been reported in three individuals [Ferguson & El-Shanti 2021].

Growth issues. Affected individuals experience failure to thrive or growth delay. This could be attributed to the elevated inflammatory markers, chronic osteomyelitis, and/or chronic anemia. Therefore, growth may not be affected in early infancy but may become apparent over time. It is unclear if anti-inflammatory treatment ameliorates the growth issues, although one affected individual did show improvement in weight and height after anti-inflammatory treatment was initiated [Rao et al 2016].

Dermatosis. Even though Sweet syndrome (neutrophilic dermatosis) was described in the initial family reported with *LPIN2*-related Majeed syndrome, skin manifestations are not common in affected individuals and sometimes may be transient. Clinical skin findings can include painful erythematous plaques, pustules, or nodules. The skin findings can occur on any part of the body, are usually patchy, and do not tend to bleed. Some affected individuals may develop erythema nodosum, which is often localized to the shins.

Gastrointestinal issues. Some affected individuals experience recurrent abdominal pain and recurrent diarrhea. However, there is limited information on these symptoms due to the small number of diagnosed individuals.

Neurodevelopment. A few affected individuals have experienced motor delay, but this has been attributed to pain due to recurrent osteomyelitis. While one case report found inflammation affecting the central nervous system [Sun et al 2021], this has not been found in other known affected individuals. There are currently no known neurologic sequelae of this condition.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The prevalence of *LPIN2*-related Majeed syndrome is unknown. To date, 32 individuals from 19 families have been reported to have molecularly proven Majeed syndrome.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *LPIN2*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *LPIN2*-Related Majeed Syndrome

Gene	Disorder	MOI	Features of This Disorder	
			Overlapping w/*LPIN2*-related Majeed syndrome	Distinguishing from *LPIN2*-related Majeed syndrome
IL1RN	Interleukin-1 receptor antagonist deficiency (OMIM 612852)	AR	Multifocal sterile osteomyelitis, ↑ ESR, ↑ CRP	Predominant skin pustulosis from early infancy
NLRP3	Chronic infantile neurologic cutaneous & articular syndrome (OMIM 607115)	AD	Recurrent fever, bone pain, skin rash	CNS involvement, chronic meningitis
PSTPIP1	Pyogenic sterile arthritis, pyoderma gangrenosum, & acne (OMIM 604416)	AD	Sterile arthritis, ↑ ESR, ↑ CRP	Acne, pyoderma gangrenosum
TNFRSF1A	TNF receptor-associated periodic fever syndrome	AD	Recurrent fever, ↑ ESR, ↑ CRP	Systemic amyloidosis, arthralgia, periorbital edema

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MOI = mode of inheritance

Acquired disorders of interest in the differential diagnosis of *LPIN2*-related Majeed syndrome

- SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome
- Chronic nonbacterial osteomyelitis

Management

No clinical practice guidelines for *LPIN2*-related Majeed syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LPIN2*-related Majeed syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *LPIN2*-Related Majeed Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To assess for failure to thrive &/or poor growth

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Radiographs or MRI of any painful &/or red, swollen limbs or joints	To assess for evidence of osteomyelitis
	Assessment for delayed motor milestones	Typically due to pain from recurrent osteomyelitis
Gastrointestinal	Physical exam to evaluate for hepatosplenomegaly	If present, abdominal ultrasound to assess degree of organomegaly
Hematologic	Measurement of CBC w/differential	To screen for microcytic anemia & neutropenia
Integument	Full skin exam	To assess for signs of dermatosis
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *LPIN2*-related Majeed syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CBC = complete blood count; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *LPIN2*-related Majeed syndrome.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended (see Table 5). With anti-inflammatory treatment, many individuals experience resolution of elevated inflammatory markers and decreased bone pain. However, there is not enough data to determine if anti-inflammatory treatment will lead to resolution of all of the features of *LPIN2*-related Majeed syndrome.

Table 5. Treatment of Manifestations in Individuals with *LPIN2*-Related Majeed Syndrome

Manifestation/Concern	Treatment [1]	Considerations/Other
Chronic multifocal or single-site sterile osteomyelitis	Anti-IL-1 therapy: • Anakinra 1.5mg/kg/day w/titration as needed • Canakinumab 2mg/kg every 4 or 8 wks	Anti-IL-1 therapy is considered the anti-inflammatory drug of choice but may not be universally available.
	Non-steroidal anti-inflammatory drugs	
	Corticosteroids (e.g., prednisone 1 mg/kg/day)	
	Methotrexate	Standard dosage typically managed by rheumatologist
Congenital dyserythropoiesis	Blood transfusion for severe anemia	• This finding may improve w/anti-inflammatory treatment. • Splenectomy may be considered.
Dermatosis	Anti-inflammatory medication (See above.)	

Table 5. continued from previous page.

Manifestation/Concern	Treatment [1]	Considerations/Other
Joint contractures / Motor delay	Standard supportive therapies, incl PT &/or OT	This finding may improve w/anti-inflammatory treatment.

Anti-IL-1 = anti-interleukin-1; PT = physical therapy; OT = occupational therapy
1. Anti-inflammatory treatment decreases inflammation and reduces flare ups.

Surveillance

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

Table 6. Recommended Surveillance for Individuals with *LPIN2*-Related Majeed Syndrome

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters	At each visit
Musculoskeletal	Assessment of joints for range of motion or contractures	
Hepatosplenomegaly	Physical exam for hepatosplenomegaly	
	Abdominal ultrasound	As clinically indicated, for those who have hepatosplenomegaly
Immunologic	ESR & CRP levels to monitor level of inflammation	At each visit
Hematologic	CBC w/differential to assess for anemia & neutropenia	Every 6 mos
Integument	Full skin exam to assess for signs of dermatosis	At each visit

CBC = complete blood count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

Agents/Circumstances to Avoid

For affected individuals managed with biologic or immunosuppressive medications, live-attenuated vaccines should be avoided, when possible.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual to identify as early as possible those who would benefit from prompt initiation of anti-inflammatory treatment. Evaluations can include:

- Targeted molecular genetic testing if the pathogenic variants in the family are known;
- If the pathogenic variants in the family are unknown, clinical assessment (history and physical exam for signs/symptoms of systemic inflammation, full skin examination for rashes, assessment of inflammatory markers [serum C-reactive protein & erythrocyte sedimentation rate], and complete blood count with differential) can be considered.

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

Pregnancy Management

Information regarding the safety of the use of anakinra in human pregnancy is limited; however, based on animal models, the use of such therapy during human pregnancy is not anticipated to lead to an increased risk of congenital anomalies in the fetus. There is no available data on the use of canakinumab during human pregnancy. However, to date there has not been a pattern of birth anomalies reported with anti-interleukin-1 medication classes.

The use of corticosteroids during human pregnancy has been associated with an increased risk of cleft lip with or without cleft palate in exposed fetuses. Medications should be discussed with a health care provider during pregnancy or when planning to conceive [Youngstein et al 2017].

Methotrexate is known to be harmful to the developing fetus and can lead to pregnancy loss and/or birth defects. Fetal outcome depends on the dose of methotrexate used, the duration of exposure, and the gestational age of the fetus during the exposure period. Methotrexate ideally should be discontinued prior to attempting to conceive.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

The clinical trial NCT02974595 is a natural history study of autoinflammatory diseases.

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.

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

LPIN2-related Majeed syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *LPIN2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *LPIN2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *LPIN2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.

- Phenotypic variability was described in a family with two affected individuals. One of the affected boys had onset of symptoms at age two years and had a severe course of illness compared to his affected first cousin, who had later onset of symptoms and a milder presentation [Rao et al 2016].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has *LPIN2*-related Majeed syndrome or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *LPIN2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *LPIN2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *LPIN2* pathogenic variants in the family.

Related Genetic Counseling Issues

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *LPIN2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Autoinflammatory Alliance**
  Phone: 415-831-8782
  Email: karen@autoinflammatory.org
  www.nomidalliance.org
- **FMF & AID Global Association**
  Familial Mediterranean Fever & Autoinflammatory Diseases
  Majeed Syndrome
- **MedLine Plus**
  Majeed syndrome

- **CRMO Foundation**
  www.crmofoundation.org
- **Systemic Autoinflammatory Diseases in India**
  India
  Information for Patients

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. LPIN2-Related Majeed Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LPIN2	18p11.31	Phosphatidate phosphatase LPIN2	LPIN2 database The registry of LPIN2 sequence variants	LPIN2	LPIN2

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 LPIN2-Related Majeed Syndrome (View All in OMIM)

605519	LIPIN 2; LPIN2
609628	MAJEED SYNDROME; MJDS

Molecular Pathogenesis

LPIN2 encodes phosphatidate phosphatase LPIN2, or lipin-2, which belongs to the lipin family of proteins and plays a key role in lipid metabolism. Lipin-2 is most abundantly expressed in the liver, small intestine, macrophages, and the central nervous system. Lipin-2 has phosphatidic acid phosphohydrolase (PAP) activity, which catalyzes the conversion of phosphatidic acid to diacylglycerol during the synthesis of triglyceride, phosphatidylcholine, and phosphatidylethanolamine. It is also involved in fatty acid metabolism and regulation of different cellular processes, including autophagy and inflammation. Lipin-2 has been shown to regulate the activity of the large multiprotein complexes known as inflammasomes, specifically NRLP3, a key component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines [Lordén et al 2017]. Lipin-2 negatively regulates the mitogen-activated protein kinases (MAPKs) and decreases the levels of pro-interleukin-1 beta. Lipin-2 also provides a lipid environment for regulating the activity of the purigenic receptor P2X7 and prevents its overactivation, thus preventing inflammation. Lipin-2 has been shown to modulate bone homeostasis independent of the inflammasome pathway by accelerating osteoclastogenesis [Bhuyan et al 2021]. Pathogenic variants in *LPIN2* cause a reduction of PAP activity, which leads to decreased lipid levels and activation of the P2X7 receptor, which in turn stimulates the NLRP3 inflammasome by potassium efflux [Lordén et al 2017].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

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