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Adenosine Deaminase 2 Deficiency

Synonyms: ADA2 Deficiency, Deficiency of Adenosine Deaminase 2 (DADA2)

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Summary

Clinical characteristics

Adenosine deaminase 2 deficiency (DADA2) is a complex systemic autoinflammatory disorder in which vasculopathy/vasculitis, dysregulated immune function, and/or hematologic abnormalities may predominate. Inflammatory features include intermittent fevers, rash (often livedo racemosa/reticularis), and musculoskeletal involvement (myalgia/arthralgia, arthritis, myositis). Vasculitis, which usually begins before age ten years, may manifest as early-onset ischemic (lacunar) and/or hemorrhagic strokes, or as cutaneous or systemic polyarteritis nodosa. Hypertension and hepatosplenomegaly are often found. More severe involvement may lead to progressive central neurologic deficits (dysarthria, ataxia, cranial nerve palsies, cognitive impairment) or to ischemic injury to the kidney, intestine, and/or digits. Dysregulation of immune function can lead to immunodeficiency or autoimmunity of varying severity; lymphadenopathy may be present and some affected individuals have had lymphoproliferative disease. Hematologic disorders may begin early in life or in late adulthood, and can include lymphopenia, neutropenia, pure red cell aplasia, thrombocytopenia, or pancytopenia. Of note, both interfamilial and intrafamilial phenotypic variability (e.g., in age of onset, frequency and severity of manifestations) can be observed; also, individuals with biallelic *ADA2* pathogenic variants may remain asymptomatic until adulthood or may never develop clinical manifestations of DADA2.

Diagnosis/testing

The diagnosis of DADA2 is established in a proband with suggestive clinical and laboratory findings and biallelic loss-of-function *ADA2* pathogenic variants identified by molecular testing and/or low (<5% of normal) or undetectable ADA2 catalytic activity in plasma or serum.

Management

Treatment of manifestations: Anti-tumor necrosis factor (TNF) agents (etanercept, adalimumab, golimumab, infliximab, certolizumab) are the drugs of choice for both symptomatic and asymptomatic individuals with

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biallelic *ADA2* pathogenic variants. They prevent and eliminate manifestations of autoinflammatory disease / vasculitis, reduce the risk of ischemic stroke, reduce inflammatory burden, and relieve immunodeficiency, hepatosplenomegaly, and neutropenia. Anti-TNF agents also improve growth and development in affected children, and red blood cell and platelet counts; however, anti-TNF agents appear to have little effect in rescuing severe bone marrow abnormalities.

Surveillance: Routine monitoring of clinical and laboratory aspects of DADA2.

Agents/Circumstances to avoid: Antiplatelet medications including aspirin; anticoagulants (except in the presence of atrial fibrillation); and smoking, which may exacerbate peripheral arterial disease.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those with biallelic *ADA2* pathogenic variants who are currently symptomatic and would benefit from prompt initiation of treatment and those who are currently asymptomatic and would benefit from treatment with anti-TNF agents to reduce the risk of stroke.

Genetic counseling

DADA2 is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier (heterozygote), and a 25% chance of being unaffected and not a carrier. Once the *ADA2* 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

Formal diagnostic criteria for adenosine deaminase 2 deficiency (DADA2) have not been established.

Suggestive Findings

Adenosine deaminase 2 deficiency (DADA2) **should be suspected** in individuals with clinical and laboratory findings of systemic autoinflammatory disease characterized by vasculitis, dysregulation of immune function, and hematologic abnormalities [Hashem et al 2017b, Lee 2018, Meyts & Aksentijevich 2018].

Systemic Autoinflammatory Disease

Clinical findings

- Intermittent fevers
- Hepatosplenomegaly (can be evidence of portal hypertension)
- Systemic hypertension

Laboratory findings

- Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate during flare episodes
- Elevated transaminases

Vasculitis

Clinical findings

- Onset. Usually in early childhood (i.e., age <10 years)
- Skin. Livedo racemosa/reticularis and/or polyarteritis nodosa and/or undifferentiated skin rash
- Neurologic. Early-onset lacunar and/or hemorrhagic strokes

Laboratory findings. Absence of antineutrophilic cytoplasmic antibodies (ANCA)

Imaging findings

- MRI
  - Acute or chronic lacunar ischemic infarcts located in the deep-brain nuclei and/or the brain stem and sparing the subcortical white matter
  - Hemorrhagic stroke and intracranial bleeding
- Angiography. Aneurysm or stenosis in medium-sized arteries

Dysregulation of Immune Function

Clinical findings

- Immunodeficiency
- Lymphoproliferative disease including lymphadenopathy

Laboratory findings

- Hypogammaglobulinemia, with low levels of IgM, IgG, and/or IgA. Low serum immunoglobulin levels may correlate with inflammatory disease activity [Schepp et al 2017].
- Impaired production of transitional and switched memory B cells
- Low vaccine responses noted in some cases
- Although T cells are largely not affected, defective T-cell proliferation, mild-to-profound CD4+ lymphopenia, and low NK counts have been reported [Trotta et al 2018].
- Positive lupus anticoagulant (present in 41% of the Authors' cohort of 41 patients who were tested – in which ascertainment could be skewed in favor of individuals with inflammatory findings) [Author, unpublished data]

Hematologic Abnormalities

Hematologic disorders typically occur early in life; however, in rare instances bone marrow failure may initially appear as late as adulthood (i.e., 5th and 6th decades):

- Lymphopenia
- Neutropenia
- Pure red cell aplasia
- Thrombocytopenia
- Pancytopenia

Bone marrow biopsy may reveal hypo/hypercellularity, grade I myelofibrosis, lymphocyte infiltrate (predominantly CD8+), and mild reticulin fibrosis, further suggesting a defect in cell differentiation. In one individual the bone marrow showed a reduced number of CD138+ plasma cells [Zhou et al 2014, Van Eyck et al 2015, Ben-Ami et al 2016, Hashem et al 2017a, Michniacki et al 2018, Trotta et al 2018].

Other

Other clinical findings include musculoskeletal features, aphthous ulcers, inflammatory bowel disease-like illness, and hearing loss.

Other laboratory findings. In contrast to individuals with an inherited deficiency of ADA, persons with DADA2 do not have profound lymphopenia and their erythrocytes have normal levels of ADA activity and undetectable (rather than elevated) levels of deoxyadenosine triphosphate or total deoxyadenosine nucleotides.

Establishing the Diagnosis

The diagnosis of DADA2 is established in a proband with suggestive findings by identification of biallelic loss-of-function *ADA2* pathogenic variants on molecular testing (Table 1) and/or low (<5% of normal) or undetectable plasma ADA2 catalytic activity. Note: While both tests are diagnostic, molecular genetic testing is more widely available.

Molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (exome sequencing, exome array, 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. Because the phenotype of DADA2 is broad, individuals with some of the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of DADA2 has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of DADA2 molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**. Among 66 individuals who were clinically suspected of having DADA2 and underwent genetic analysis at a French referral center for autoinflammatory disorders, 13 individuals from 11 families (20%) were found to have biallelic *ADA2* pathogenic variants [Rama et al 2018]. Among those with DADA2, more than 80% had a combination of a biomarker of inflammation (fever, elevated CRP), evidence of vasculitis (cutaneous, neurologic), and more than one clinical flare. Of note, these criteria may not apply to individuals who present with hematologic manifestations only [Ben-Ami et al 2016, Sönmez et al 2018].

Single-gene testing. Sequence analysis of *ADA2* detects biallelic, homozygous or compound heterozygous, missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. In individuals with a highly suspicious clinical presentation and or/low plasma/serum ADA2 activity in whom only one or no pathogenic variant is found, performing gene-targeted deletion/duplication analysis may detect intragenic deletions or duplications (i.e., copy number variants).

A multigene panel that includes *ADA2* and other genes associated with immune dysregulation, primary immunodeficiency, or autoinflammatory syndromes (see Differential Diagnosis) is most likely to identify a genetic cause 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) Some laboratories offer custom-designed panels and/or 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 diagnosis of DADA2 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 DADA2 has not been 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 the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If

exome sequencing identifies only one *ADA2* pathogenic variant, perform **exome array** (when clinically available) to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Adenosine Deaminase 2 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ADA2	Sequence analysis [3]	~97% [4]
	Gene-targeted deletion/duplication analysis [5]	~3%% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Hashem et al [2017b], Meyts & Aksentijevich [2018]
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. Zhou et al [2014], Fellmann et al [2016], Uettwiller et al [2016], Lee et al [2018], Grossi et al [2019]

ADA2 enzyme activity. In humans, the enzyme ADA2 is present in plasma and myeloid cells, but not in erythrocytes. DADA2 is associated with low (<5% of normal) or absent ADA2 enzymatic activity in serum or plasma (fresh or stored frozen samples). DADA2 can also be diagnosed by measuring ADA2 activity in extracts of dried plasma spots on filter paper [Ben-Ami et al 2016]. The two biochemical assays used are ELISA (enzyme-linked immunosorbent assay) and HPLC (high-performance liquid chromatography).

Note: (1) An ELISA-based assay for ADA2 activity is commonly used in research laboratories but may not be available in clinical laboratories; (2) although deficiency of immuno-precipitable ADA2 enzyme has been demonstrated in persons with DADA2 [Zhou et al 2014], no anti-ADA2 antibody-based method has been validated for use in clinical laboratories.

Clinical Characteristics

Clinical Description

Deficiency of adenosine deaminase 2 (DADA2) is a systemic autoinflammatory disorder in which the three major manifestations are vasculitis, dysregulation of immune function, and hematologic disease [Hashem et al 2017b, Lee 2018, Meyts & Aksentijevich 2018]. Other clinical features include neurologic, gastrointestinal, and musculoskeletal involvement. Severe manifestations (e.g., strokes or ischemic injuries to tissues and/or organs) can cause disability and/or be life threatening. Prior to the discovery of the molecular pathogenesis of DADA2 and adequate therapies, death before age 30 years was reported in 8% of affected individuals [Hashem et al 2017b, Meyts & Aksentijevich 2018].

Phenotypic variability that cannot be fully explained by the effect of pathogenic variants on protein function can be observed in the same family; for example, one sib may have have early-childhood onset of manifestations whereas another may have later-childhood onset. Affected individuals homozygous for the same founder variant have variability in age of onset and in frequency and severity of manifestations [Van Montfrans et al 2016]. In a large family of Iraqi descent, four adults homozygous for the same pathogenic variant were symptom free despite low ADA2 activity [Nanthapisal et al 2016].

Vasculitis

The most frequent manifestations of DADA2 are related to arterial vasculopathy which often manifests as cutaneous lesions. Cutaneous manifestations, reported in more than 75% of affected individuals, include livedo racemosa/reticularis, polyarteritis nodosa (PAN), subcutaneous nodules, cutaneous ulcers, or lupus-like rash [Gonzalez Santiago et al 2015, Caorsi et al 2016, Skrabl-Baumgartner et al 2017].

Histopathologic findings of DADA2-associated PAN and PAN of unknown cause are the same: non-granulomatous, necrotizing vasculitis of small and medium-sized vessels. Sometimes less specific findings are interpreted as leukocytoclastic vasculitis. In younger individuals with livedoid rash, skin biopsy shows interstitial neutrophil and macrophage infiltration without overt vasculitis.

In one study, nine (15%) of 60 children with PAN, cutaneous PAN, unclassifiable vasculitis (UCV), young-onset chronic vasculitis, or history of stroke were found to have biallleic *ADA2* pathogenic variants. Previous clinical diagnoses included PAN (5 children), UCV (3), and ANCA-associated vasculitis (1) [Gibson et al 2019].

Ischemic strokes are often observed in (but not limited to) the brain stem, thalamus, basal ganglia, and internal capsule [Bulut et al 2019]. These small infarcts, described as lacunar strokes, may not always be observable on MRI.

Over time accumulation of the effects of these small initially undetectable strokes can lead to severe neurologic impairments such as persistent dysarthria, ataxia, palsy of one or more cranial nerves, and cognitive impairment [Springer et al 2018].

Other neurologic manifestations can include the following:

- Small, deep intracerebral hemorrhage. Specifically, hemorrhagic strokes were observed on MRI and/or CT in the ventricular system and right frontal insula in different individuals. Most often they occur in the setting of concomitant use of antiplatelet or anticoagulant therapy; however, on rare occasion they may occur spontaneously [Belot et al 2014, Garg et al 2014, Navon Elkan et al 2014, Zhou et al 2014, Nanthapisal et al 2016, Lee et al 2018].
- Cerebral vessel aneurysm (1 patient) [Navon Elkan et al 2014]
- Seizures resulting from strokes. Manifestations are related to the location of the stroke.
- Central and peripheral neuropathy. The diverse manifestations reported include cranial nerve palsies, sensorineural hearing loss, and ophthalmologic complications [Lee 2018].

Other effects of distal artery occlusion include peripheral vascular insufficiency, digital necrosis, and Raynaud phenomena [Navon Elkan et al 2014, Zhou et al 2014].

GI manifestations generally include abdominal pain and chronic gastritis. On rare occasions, intestinal necrosis, bowel perforation, and arterial stenosis are observed [Belot et al 2014, Batu et al 2015].

Hepatic disease involves hepatomegaly and splenomegaly that can lead to portal hypertension and associated esophageal varices. Histopathologic findings include evidence of nodular regenerative hyperplasia and/or hepatic sclerosis that can potentially lead to end-stage liver disease [Springer et al 2018].

Other organs with dense vascularization such as the kidney can be affected. Multiple aneurysmal dilatations and variation in the caliber of medium-small intrarenal arteries have been reported as well as renal artery stenosis and infarcts [Navon Elkan et al 2014, Nanthapisal et al 2016, Sahin et al 2018].

Dysregulation of Immune Function

General dysregulation of immune function can include immunodeficiency, lymphoproliferative disease, and autoimmune manifestations of varying severity.

Immunodeficiency. While the autoinflammatory phenotype was predominant in the initial description of DADA2, mild immunodeficiency was identified in five of nine patients in the cohort [Zhou et al 2014]. Intially it was not clear if immunodeficiency could be related to the use of immunosuppressive therapies; however, subsequently in the German cohort of 181 individuals with antibody deficiency and/or features of common variable immunodeficiency, eleven individuals were found to have DADA2 [Schepp et al 2016, Schepp et al 2017]; of these, four presented with immunodeficiency without vascular manifestations. To date the spectrum of immunodeficiency includes variable degrees of B-cell depletion and hypogammaglobulinemia. T-cell numbers are largely unaffected except in patients with bone marrow failure.

About 20% of individuals with DADA2 experience bacterial and/or viral infections resulting from immunodeficiency. Bacterial infections typicaly involve the upper- and lower-respiratory tract, gastrointestinal tract, and urinary tract. Viral infections have included recurrent herpes simplex infections, skin warts (caused by the human papilloma virus) [Arts et al 2018], and in one child, shingles (caused by the herpes zoster virus) [Ghurye et al 2019].

Although fungal and mycobacterial infections are unusual, they were observed in one individual with severe monocytopenia [Hsu et al 2016] and in two sibs with a contiguous gene deletion involving *ADA2* and *IL-17RA* in whom recurrent fungal infections were attributed to IL-17R deficiency [Fellmann et al 2016].

Lymphoproliferative disease. Generalized lymphadenopathy is seen in more than 10% of affected individuals; splenomegaly is fairly common. The lymphoproliferative phenotype of DADA2 can include the following:

- Features mimicking the following disorders:
  - GATA2 deficiency [Hsu et al 2016]
  - Autoimmune lymphoproliferative syndrome (ALPS) [Alsultan et al 2018, Barzaghi et al 2019]
  - Multicentric Castleman disease [Van Nieuwenhove et al 2018]
- CD3+ CD8+ T-cell large granular lymphocytic (T-LGL) infiltration of the bone marrow (in 2 individuals) [Trotta et al 2018].
- Adolescent-onset Hodgkin's lymphoma (HL) was initialy reported in one individual (however, definitive supporting evidence for HL was not available) [Springer et al 2018]. More recently, childhood-onset HL was histopathologically confirmed in two sibs with DADA2 [Alabbas et al 2019].

Autoimmune disease resembling systemic lupus erythematosus and autoimmune cytopenia was reported in two unrelated families [Schepp et al 2016, Skrabl-Baumgartner et al 2017].

Hematologic Disease

Hematopoietic complications include variably decreased numbers of leukocytes, platelets, and erythrocytes (including pure red cell aplasia [PRCA] similar to Blackfan-Diamond anemia), as well as pancytopenia due to complete bone marrow failure. A meta-analysis of published data on 161 individuals with DADA2 revealed anemia in 13%, neutropenia in 7%, and thrombocytopenia in 6%, whereas leukopenia, PRCA, NK cell deficiency, and pancytopenia were observed in fewer than 5% [Meyts & Aksentijevich 2018].

The initial clinical presentation in five children from four unrelated consanguineous families was PRCA and hemolytic anemia without manifestations of inflammation or vasculitis [Ben-Ami et al 2016].

Neutropenia was severe (i.e., low or absent absolute neutrophil counts) in two affected individuals [Hashem et al 2017a, Cipe et al 2018] and moderate but persistent in other affected individuals [Ghurye et al 2019].

Musculoskeletal Manifestations

About 40% of affected individuals have the following musculoskeletal manifestations: myalgia/arthralgia (22%), arthritis (14%), and myositis (1%) [Meyts & Aksentijevich 2018, Sahin et al 2020]. Musculoskeletal

manifestations are often accompanied by other features of systemic inflammation, such as fevers and/or elevated acute-phase reactants.

Genotype-Phenotype Correlations

To date no genotype-phenotype correlations associating ADA2 pathogenic variants with the clinical presentation of DADA2 have been identified.

Studies of affected individuals in the two major founder populations in the Middle East and northern Europe could possibly offer insight into some genotype-phenotype correlations. See Table 3 for more details.

- The p.Gly47Arg founder variant, identified in 19 individuals of Georgian-Jewish ancestry and 15 individuals of Turkish ancestry, was associated with the clinical diagnosis of childhood-onset cutaneous polyarteritis nodosa (despite some clinical variability).
- The p.Arg169Gln founder variant identified in nine Dutch individuals was associated with significant variability in disease onset as well as frequency and severity of manifestations among affected sibs [Van Montfrans et al 2016]. Compared to the p.Gly47Arg variant, the cutaneous and visceral manifestations associated with the p.Arg169Gln variant in general were less severe, whereas neurologic and hematologic manifestations were more common.
- In a large family of Iraqi descent two affected and four unaffected members homozygous for the pathogenic missense variant p.Pro251Leu had low ADA2 activity irrespective of disease status, indicating variable expressivity of the clinical features of DADA2 [Nanthapisal et al 2016].

Prevalence

DADA2 is considered a rare disease; however, since its initial description in 2014, more than 170 affected individuals have been reported in the literature. Based on allele frequencies of in silico-predicted *ADA2* damaging variants, the estimated prevalence of DADA2 could be as high as 4:100,000.

DADA2 prevalence is higher in populations with a high degree of consanguinity or in populations with founder variants. See Table 3.

- Most affected individuals from the Middle East are homozygous for the p.Gly47Arg founder variant. The highest carrier frequency for this variant is reported in the Georgian-Jewish population (1:10); the estimated carrier frequency of this variant in the Turkish population is about 1:500.
- The p.Arg169Gln founder variant has an estimated carrier frequency of 1:500 in northern European populations (Finnish, Dutch). The allele frequency is significantly lower in African, Latino, and Asian populations.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ADA2*.

Differential Diagnosis

Inherited disorders to consider in the differential diagnosis of DADA2 are included in Table 2; disorders without a known genetic component to consider in the differential diagnosis are discussed following Table 2.

Table 2. Inherited Disorders with Normal ADA2 Enzyme Activity to Consider in the Differential Diagnosis of Adenosine Deaminase 2 Deficiency (DADA2)

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/DADA2	Distinguishing from DADA2
Diamond-Blackfan anemia (DBA)	12 ribosomal protein genes, *GATA1*, *TSR2*	AD	Pure red cell aplasia	May have microcephaly, cleft palate & distinctive facies (hypertelorism, broad flat nasal bridge)
ADA-SCID [1]	*ADA*	AR	Immune deficiency	• Immune deficiency is much more severe. • Depletion of T, B, & NK cells • Low levels of ADA • Lack cerebrovascular disease & cutaneous manifestations
GATA2 deficiency (OMIM 614172)	*GATA2*	AD	Immune deficiency, cytopenia, recurrent infections [2]	• Infections are often invasive. • Vasculitic complications are rare.
Autoimmune lymphoproliferative syndrome (ALPS)	*CASP10*, *FAS*, *FASLG* [3]	AD AR	Lymphadenopathy, splenomegaly, immune-mediated cytopenia [4]	ALPS, caused by primary defect in programmed cell death, has more autoimmune features.

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance
1. ADA-SCID = severe combined immune deficiency caused by adenosine deaminase defects
2. Hsu et al [2016]
3. Approximately 20%-25% of individuals with ALPS lack a genetic diagnosis (see ALPS).
4. Alsultan et al [2018]

Disorders with normal ADA2 enzyme activity and without a known genetic component include the following:

- **Polyarteritis nodosa** characterized by vasculitis/vasculopathy, livedo, skin nodules and aneurysms of medium-sized arteries. Features of DADA2 not observed are strokes, hematologic disorders, and immune deficiency.
- **Sneddon syndrome** characterized by livedo racemosa, Raynaud phenomenon, and noninflammatory thrombotic cerebral vasculopathy. It can be associated with systemic lupus erythematosus and antiphospholipid syndrome (antiphospholipid antibodies are detected in ~50% of affected individuals). It is more common in women and onset is usually in or after the second decade of life. While most occurrences are simplex cases (i.e., a single occurrence in a family), some individuals have a positive family history consistent with autosomal dominant inheritance [Goel et al 1999, Hademenos et al 2001, Szmyrka-Kaczmarek et al 2005].
- **Autoimmune neutropenia** characterized by absolute to low neutrophil counts. It is often present in persons with systemic lupus erythematosus or other autoimmune diseases. Of note, in autoimmune diseases, neutropenia is mediated by autoantibodies and other clinical features of DADA2 are absent; in contrast, in DADA2 the mechanism of neutropenia is unclear.
- **CVID.** About 5%-6% of individuals diagnosed with common variable immunodeficiency (CVID) and antibody deficiency were found to have DADA2 on molecular genetic testing [Schepp et al 2017].
- **Myalgia/myositis, fibromyalgia, and arthralgia/arthritis** observed in about 20% of individuals with DADA2 resemble the findings of juvenile idiopathic arthritis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with adenosine deaminase 2 deficiency (DADA2), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

- **Complete physical examination** with emphasis on:
  - Blood pressure and other vital signs, as systemic hypertension and/or fever are common.
  - Skin examination for evidence of livedo reticularis/racemosa, nodules, and Raynaud phenomenon. Severe involvement can include digital infarcts/gangrene or skin ulcerations.
  - Assessment for lymphadenopathy and hepatosplenomegaly.
  - Neurologic examination for evidence of prior or recent strokes.
- **Ophthalmologic examination** for vision loss, diplopia, retinal infarcts, optic nerve damage, uveitis, ptosis, strabismus, and nystagmus
- **Electrocardiogram** (ECG) for manifestations of portal hypertension, including prolonged QT interval
- **Laboratory assessment**
  - Complete blood count (CBC) with differential to detect anemia, lymphopenia, neutropenia, and/or thrombocytopenia
  - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as elevated levels may correlate with disease activity
  - Kidney and liver function tests
  - Quantitative serum immunoglobulins
  - PT/PTT to assess the risk of stroke in a patient who has not had a stroke OR to assess the risk of subsequent strokes in those who have had a stroke
  - Autoantibodies including antinuclear antibodies and lupus anticoagulant. Low titers are reported in 10% of patients, whereas high titers suggest other autoimmune diseases, such as systemic lupus erythematous.
  - Antineutrophilic cytoplasmic antibodies (ANCA) are usually absent; their presence suggests ANCA-related vasculitis.
  - Lymphocyte phenotyping. Failure to develop memory B-cells, a common finding, is evidence of a B-cell maturation defect that warrants further evaluation of the immune system (quantitative serum immunoglobulins, antibody response to vaccines, and history of severe and/or multiple infections). Failure to develop memory T-cells may be seen but is uncommon.
  - Antibody response to vaccines. Inadequate response suggests immune deficiency.
- **Imaging assessment**
  - Brain MRI in all patients, even those without overt neurologic manifestations, as a baseline given that small strokes can be clinically silent
  - Magnetic resonance angiography (MRA):
    - When brain MRI is abnormal, brain MRA (which is expected to be normal in persons with DADA2) can help differentiate the cause of stroke.
    - Abnormal peripheral MRA may suggest additional treatment options to improve vascular flow for cutaneous lesions (e.g., vascular insufficiency, infarcts, gangrene) or neurologic dysfunction, such as peripheral neuropathy).
  - Renal ultrasound examination to assess kidney size (which can be smaller due to poor vascularization and/or infarcts), function, and blood flow. Reported abnormalities that merit documentation before intiation of treatment include renal artery aneurysm and stenosis, renal

infarcts (which may be silent), renal inflammation with dense lymphocytic infiltration, and glomerular scarring.
    - Abdominal ultrasound examination to provide baseline assessment of liver and spleen size and hepatic blood flow. Splenomegaly occurs in up to 30% of affected individuals, hepatomegaly in 20%.
    - FibroScan® ultrasound examination (if available) to assess baseline hepatic elasticity (because early portal hypertension can be clinically silent)
- **Other**
    - When clinically indicated:
        - Skin biopsy in order to document vasculitis, or to investigate an atypical rash
        - Liver biopsy to assess cause of hepatomegaly and presence of hepatic steatosis and/or nodular regenerative sclerosis
    - Evaluation for manifestations of portal hypertension. If present, perform endoscopy to assess its extent.
- **Consultation with a clinical geneticist and/or genetic counselor**

Treatment of Manifestations

Current Treatment for Persons with Symptomatic DADA2

Anti-tumor necrosis factor (TNF) agents (also known as "biologics") including etanercept, adalimumab, golimumab, infliximab, and certolizumab are the drugs of choice to prevent and eliminate manifestations of autoinflammatory disease / vasculitis. Use of such drugs reduces risk of ischemic stroke and inflammatory burden (as shown by lower CRP/ESR levels and less skin rash) and relieves immunodeficiency, hepatosplenomegaly, and neutropenia. In a cohort of 15 patients with DADA2 who had a total of 37 strokes before the initiation of anti-TNF therapy, no strokes were observed post treatment [Ombrello et al 2019]. Use of such drugs also increases growth and development in affected children, and improves red blood cell and platelet counts due to relief of the inflammatory burden. Of note, anti-TNF agents appear to have little effect in rescuing severe bone marrow abnormalities.

Some individuals with low serum immunoglobulins and frequent infections may require treatment with intravenous immunoglobulin as well as antibiotics and antivirals in conjunction with anti-TNF agents [Hashem et al 2017c, Schepp et al 2017].

Methotrexate is added when administering adalimumab or infliximab to prevent development of drug-related antibodies.

Thalidomide is a potential treatment for TNF blockade when biologics are not available. Thalidomide is known to inhibit TNF production in dendritic cells and to exert an inhibitory effect on monocytes [Deng et al 2003]. Of note, in a study of six patients, all responded completely to thalidomide treatment; subsequently, however, the drug had to be discontinued (after treatment ranging from 20 months to 5 years) in three of the six due to neurologic toxicity [Caorsi et al 2017]. A study evaluating long-term thalidomide treatment in patients with multiple myeloma characterized neurologic toxicity as sensory peripheral neuropathy, including paraesthesias, tremor, and dizziness [Tosi et al 2005].

Steroids and general immunosuppressive therapies (e.g., azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate mofetil, and tacrolimus) have had variable success.

Anti-IL-6 therapy was successfully used in a patient with DADA2 whose manifestations mimicked multicentric Castleman disease [Van Nieuwenhove et al 2018].

Hematopoietic stem cell transplantation (HSCT) can be curative in individuals in whom bone marrow failure and/or immune dysregulation predominate, and who fail to respond to TNF inhibitor treatment. Successful

HSCT returns plasma ADA2 activity to normal levels. In one study the hematologic and immunologic phenotype resolved post HSCT in all 14 patients with bone marrow dysfunction or immunodeficiency (6 of whom also had vasculitis); however, acute and moderate chronic autoimmunity and graft-versus-host disease were reported [Hashem et al 2017c].

Current Treatment for Asymptomatic Persons with Biallelic DADA2-Causing Variants in *ADA2*

Currently there are no predictors of which individual with biallelic *ADA2* pathogenic variants will develop a stroke or when a stroke may occur. Because of the potentially devastating consequences of stroke, the authors treat all individuals who have biallelic *ADA2* pathogenic variants with anti-TNF agents to reduce the risk of stroke.

Surveillance

Suggested follow-up evaluations include the following:

- Complete physical examination (performed yearly or sooner if clinically indicated):
  - Blood pressure and other vital signs
  - Skin examination
  - Assessment for presence of lymphadenopathy and hepatosplenomegaly
  - Neurologic examination for evidence of prior or recent strokes
- Ophthalmologic examination for ptosis, abnormal eye movements, retinal infarcts, optic nerve damage
- ECG (if abnormal in the past). Note: Arterial hypertension, reported in 20% of patients, can lead to myocardial dysfunction.
- Laboratory assessment (performed yearly or sooner if clinically indicated):
  - CBC and differential
  - ESR and CRP
  - Kidney and liver function
  - Quantitative serum immunoglobulins
  - Lymphocyte phenotyping for evidence of a B-cell maturation defect
  - Additionally, follow-up evaluation of abnormal laboratory studies identified at earlier evaluations
- Imaging assessment (yearly or if clinically indicated):
  - Brain MRI if abnormal in the past or new symptoms or manifestations suggest brain involvement
  - Peripheral MRA if symptoms of peripheral arterial disease and/or neurologic dysfunction
  - Abdominal ultrasound examination to assess liver, spleen, and kidney size and hepatic blood flow
  - FibroScan® ultrasound examination (if available) to assess hepatic elasticity for evidence of early portal hypertension
- Liver biopsy (if clinically indicated) is the most reliable way to diagnose diffuse hepatic disease (e.g., in the presence of portal hypertension).

Agents/Circumstances to Avoid

Avoid the following:

- Antiplatelet medications including aspirin
- Anticoagulation medications (except in the presence of atrial fibrillation)
- Smoking, which may exacerbate peripheral arterial disease

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those with biallelic *ADA2* pathogenic variants who are currently symptomatic and would benefit from prompt initiation of treatment and those who are currently asymptomatic and would benefit from treatment with anti-TNF agents to reduce the risk of stroke.

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

Pregnancy Management

Information regarding the safety of use of anti-TNF agents during pregnancy is limited. One study evaluating use of anti-TNF agents in pregnant women with inflammatory bowel disease determined that these drugs can cross the placenta from the latter part of the second trimester of gestation, though they are low risk in the short term [Gisbert & Chaparro 2013].

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

Adenosine deaminase 2 deficiency (DADA2) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ADA2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not thought to be at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not thought to be at risk of developing the disorder.

Offspring of a proband. Unless an individual with DADA2 has children with an affected individual or a carrier (see Prevalence), his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ADA2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ADA2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ADA2* 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, clarification of carrier 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, are carriers, or are at risk of being carriers.

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 the *ADA2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **DADA2 Foundation**
  Email: info@dada2.org
  www.dada2.org
- **Immune Deficiency Foundation**
  Phone: 800-296-4433
  Fax: 410-321-9165
  Email: idf@primaryimmune.org
  primaryimmune.org
- **ImmUnity Canada**
  Canada
  Phone: 877-607-2476 (toll-free)
  Email: info@immunitycanada.org
  immunitycanada.org
- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**
  United Kingdom
  Phone: +44 01503 250 668
  Fax: +44 01503 250 668
  Email: info@ipopi.org

ipopi.org

- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.org
- **Vasculitis Foundation**
  PO Box 28660
  Kansas City 64188
  Phone: 816-436-8211; 800-277-9474
  Fax: 816-656-3838
  www.vasculitisfoundation.org
- **DADA2 Foundation Registry**
  www.dada2.org/registry
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **RDCRN Patient Contact Registry: Primary Immune Deficiency Treatment Consortium**
  Patient Contact Registry
- **United States Immunodeficiency Network (USIDNET) Registry**
  Email: contact@usidnet.org
  Enrolling Institutions

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. Adenosine Deaminase 2 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ADA2	22q11.1	Adenosine deaminase 2	ADA2	ADA2

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 Adenosine Deaminase 2 Deficiency (View All in OMIM)

607575	ADENOSINE DEAMINASE 2; ADA2
615688	VASCULITIS, AUTOINFLAMMATION, IMMUNODEFICIENCY, AND HEMATOLOGIC DEFECTS SYNDROME; VAIHS

Molecular Pathogenesis

Humans express two enzymes, ADA1 (also referred to as ADA) (see Adenosine Deaminase Deficiency) and ADA2, which catalyze the deamination of adenosine and 2'-deoxyadenosine to inosine and deoxyinosine, respectively. Although homologous proteins that are considered isozymes, ADA1 and ADA2 differ substantially in structure, including the arrangement of the substrate-binding pocket in the catalytic center [Zavialov et al 2010b]. As a result, the affinity of ADA2 for adenosine is 100-fold lower than that of ADA1.

ADA1 is a largely intracellular protein, whereas ADA2 is a secreted protein. It has been postulated that ADA2 may control the level of extracellular adenosine (generated by stepwise dephosphorylation of extracellular ATP

and AMP) and regulate a variety of biologic processes (through 4 distinct adenosine receptors expressed on many cells in the brain and immune and cardiovascular systems).

- **Activation.** Under stress conditions, hypoxia, ischemia, or inflammation, adenosine concentration increases due to excessive ATP breakdown.
- **Signal termination.** Adenosine signaling is terminated by adenosine uptake from the extracellular space towards the intracellular space through nucleoside transporters, followed by metabolic conversion in the presence of adenosine kinase (to AMP) or deaminase (to inosine). Thus, the deamination step is critical for regulation of many signaling pathways including immune responses.

Gene structure. *ADA2* spans about 43,000 base pairs and comprises ten exons. The codon for translation initiation (p.1Met) is located in exon 2.

See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants are loss of function. The majority of pathogenic variants are missense variants; however, nonsense and splice site variants as well as small and large deletions have also been reported. Pathogenic missense variants are located in different regions of the gene and do not cluster to a specific exon.

Table 3. Notable *ADA2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001282225.1 NP_001269154.1	c.139G>A	p.Gly47Arg	Founder variant in Israeli, Georgian-Jewish, & Turkish populations [Hashem et al 2017b]
	c.140G>C	p.Gly47Ala	Found in multiple populations
	c.506G>A	p.Arg169Gln	Founder variant in persons of Finnish or Dutch ancestry [Van Montfrans et al 2016]
	c.752C>T	p.Pro251Leu	Low ADA2 activity w/variable expressivity of clinical features [Nanthapisal et al 2016]
	c.1078A>G	p.Thr360Ala	Found more commonly in persons of Italian ancestry [Caorsi et al 2017]
	c.1358A>G	p.Tyr453Cys	Most common pan ethnic variant [Hashem et al 2017b]
	c.973-2A>G	Aberrant mRNA splicing	Found in multiple populations

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. ADA2 is a 59-kd monomer protein made up of 511 amino acids. It has four domains:

- Dimerization
- Catalytic
- Putative receptor binding
- Substrate binding

ADA2 forms a homodimer and localizes to the extracellular space where it may reduce the extracellular adenosine concentration.

ADA2 has four aspargine glycosylation sites at p.Asn127, p.Asn174, p.Asn185, and p.Asn378 [Zavialov et al 2010a]. Glycosylation plays an important role in ADA2 secretion by modulating ADA2 trafficking from the endoplasmic reticulum (ER) to the Golgi. Alteration of one consensus glycosylation sequence constituted by

p.Thr129 and p.Asn127 has been shown to lead to ER retention and defective secretion of the abnormal ADA2 [Lee et al 2018].

ADA2 is predominately expressed in myeloid cells such as monocytes, macrophages, and dendritic cells. ADA2 is secreted by activated myeloid cells. Although it has been postulated that ADA2 decreases extracellular adenosine concentration at the sites of inflamed or tumor tissues, this has not been shown either in vitro or in vivo. Where measured, adenosine has not been elevated in the plasma of individuals with DADA2 [Van Eyck et al 2015], in contrast to the elevated levels found in individuals with ADA deficiency (see Adenosine Deaminase Deficiency). Numerous studies report elevated levels of ADA2 in the serum of individuals with HIV and chronic inflammatory diseases, as well as in tuberculous pleural effusions.

ADA2 has homology to so-called adenosine deaminase growth factors (ADGFs) identified in several insect species, fish, and frogs. Although ADA2 is found in many species, mice lack an *ADA2* ortholog, which has hampered in vivo studies of ADA2 function. ADGFs may control tissue growth by modulating the level of extracellular adenosine [Zurovec et al 2002, Zavialov et al 2010a]. ADA2 also binds proteoglycans and adenosine receptors on immune cells, implying a role in cell signaling.

The role of ADA2 in multilineage hematopoiesis remains unclear. It is unknown if ADA2 plays additional roles in the development of bone marrow precursors or if the bone marrow failure in DADA2 may be related to inflammatory cell infiltration [Meyts & Aksentijevich 2018].

Abnormal gene product. Pathogenic missense variants are found in all protein domains and may affect protein secretion, dimerization or catalytic activity. Essentially, all pathogenic variants lead to decreased or complete loss of ADA2 protein expression and catalytic activity, one of the diagnostic features of DADA2. Lack of protein activity compromises several cellular processes that contribute to DADA2 pathogenesis (see Molecular Pathogenesis).

In ADA2 deficiency an imbalance between anti-inflammatory M2 and proinflammatory M1 macrophages may create a hyper-inflammatory environment that is damaging to blood vessels [Zhou et al 2014]. Another study showed that adenosine can induce formation of neutrophil extracellular traps and also identified circulating low-density granulocytes, suggesting that neutrophils further contribute to the inflammatory phenotype [Carmona-Rivera et al 2019]. Activated myeloid cells can inflict damage to endothelial cells, causing vasculopathy/vasculitis. This effect of the ADA2-deficient myeloid cells on endothelial cells can be reversed with treatment with anti-TNF agents (see Treatment of Manifestations).

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Chapter Notes

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