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Haploinsufficiency of A20

Synonym: HA20

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Summary

Clinical characteristics

Haploinsufficiency of A20 (HA20), a complex immune dysregulation disease, is characterized by recurrent systemic immune dysfunction (i.e., inflammation and/or immune deficiency). The most common manifestations and their frequency include: (1) recurrent painful oral/genital ulcers, typically during disease flares (>70% of persons); (2) recurrent fevers (~50%), typically lasting for three to seven days that can rarely progress to a cytokine storm and/or hemophagocytic lymphohistiocytosis; (3) skin involvement (~40%), including pustular rashes, folliculitis, vasculitic purpura, urticaria, lupus-like macular rashes, and eczematoid dermatitis; (4) gastrointestinal disease (~40%), ranging from dull abdominal pain (due to serositis, ulcers, or bowel inflammation) to severe inflammation with risk of bowel perforation; and (5) arthralgia/arthritis (~34%), typically relapsing and/or remitting nonerosive inflammatory polyarthritis with synovitis, and rarely resembling rheumatoid arthritis or psoriatic-like erosions. Other less common but significant findings include lymphoproliferation, most often lymphadenopathy; liver involvement, including severe hepatitis that if untreated can progress to cirrhosis and liver failure; neurologic disease including central nervous system vasculitis/vasculopathy (manifesting as severe headaches and cognitive changes) and in some individuals transient ischemic attacks. Other findings include aseptic meningitis, mononeuritis multiplex, chronic inflammatory demyelinating polyradiculoneuropathy, and/or peripheral neuropathy.

HA20 demonstrates both variable expressivity (i.e., different systems may be involved simultaneously and/or over time in an affected individual) and intrafamilial variability (i.e., variability in clinical presentation among affected individuals within the same immediate or extended family).

Diagnosis/testing

The diagnosis of HA20 is established in an individual by identification of either a heterozygous *TNFAIP3* pathogenic variant (~95% of affected individuals) or a heterozygous deletion of 6q23 including *TNFAIP3* (<5% of affected individuals) by molecular genetic testing.

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Management

Supportive treatment: TNF inhibitors, the most used medications, directly target abnormal NF-κB signaling. In addition, IL-1 targeted therapy and JAK inhibitors are effective in many individuals. Corticosteroids, colchicine, methotrexate, azathioprine, thalidomide, mycophenolate, phosphodiesterase-4 inhibitors, and calcineurin inhibitors may also be useful. In some instances of severe or refractory disease, hematopoietic stem cell transplantation may be considered.

Surveillance: Monitor at least annually by a rheumatologist, and more frequently for individuals with evidence of systemic inflammation and/or organ involvement. Typical evaluations include medical history, physical examination, and laboratory testing of acute phase reactants including CRP, ESR, fibrinogen, CBC with differential, SAA, and urinalysis for evidence of proteinuria. Low threshold for evaluation of subclinical inflammation by relevant subspecialists, such as gastroenterologist for inflammatory bowel disease-like symptoms, neurologist for aseptic meningitis, and ophthalmologist for symptoms of ocular inflammation.

Agents/circumstances to avoid: For individuals managed with continuous biologic agents, consideration should be given to whether live attenuated versus non-live vaccines should be administered. Because data are limited on the effect of live attenuated vaccines, risks/benefits should be considered before receiving any live vaccinations.

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 an initial evaluation similar to that of a symptomatic individual and prompt initiation of treatment and/or scheduled routine surveillance.

Pregnancy management: Maternal medications should be discussed with a health care provider ideally prior to conception or as soon as a pregnancy has been recognized. Colchicine is generally considered safe during pregnancy; however, data are limited. Information regarding the safety of the use of TNF inhibitors in human pregnancy is limited. Per the American College of Rheumatology guidelines for general populations, the use of anti-TNF agents is recommended for women with active disease, with consideration of weaning such medication during the third trimester if maternal remission has been achieved to decrease placental transfer to the fetus. The IL-1 receptor antagonist anakinra is considered relatively safe during pregnancy due to its extremely short half-life, although data are limited. JAK inhibitors are contraindicated during pregnancy.

Genetic counseling

HA20 is inherited in an autosomal dominant manner. Many individuals diagnosed with HA20 have an affected parent; some individuals have the disorder as the result of a *de novo* *TNFAIP3* pathogenic variant. Each child of an individual with HA20 has a 50% chance of inheriting the *TNFAIP3* pathogenic variant. Once the *TNFAIP3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus diagnostic criteria for haploinsufficiency of A20 (HA20) have been published.

Suggestive Findings

HA20 **should be suspected** in probands with the following clinical and laboratory findings and family history.

Clinical findings

- **All individuals**

- Mean age of onset is 7 years (range: 1st week of life to age 39 years) [Yu et al 2020]

  Note: Because of variable expressivity, manifestations during early childhood may not have been reported to a health care professional due to their mildness and minimal effect on quality of life, or due to social barriers (i.e., genital ulcers).

- Relapsing/remitting disease course characterized by unprovoked episodes of acute or chronic immune dysregulation

- **Common** (present in ≥15% of individuals)
  - Episodic fever
  - Recurrent painful ulcers/abscesses, including oral (~68%), genital (~37%), perianal, cutaneous, and gastrointestinal (~39%; sometimes diagnosed as Crohn disease or inflammatory bowel disease-related arthritis, can lead to bowel obstruction)
  - Arthralgia/polyarthritis, including polyarticular juvenile idiopathic arthritis and erosive arthritis (~34%)
  - Cutaneous lesions, including folliculitis-like rashes, acne, and dermal abscesses, psoriasis, erythema nodosum, and immunoglobulin A vasculitis (Henoch-Schonlein purpura) (~42%)
  - Lymphadenopathy (25%-30%)
  - Autoimmune cytopenias (~20%)

- **Less common** (present in ≤15% of individuals)
  - Chronic hepatic involvement, including hepatitis, hepatomegaly, and/or liver fibrosis (15%)
  - Autoimmune thyroiditis (~14%)
  - Neurologic involvement, including chronic inflammatory demyelinating polyradiculoneuropathy, neuropathy, and central nervous system vasculitis (~12%)
  - Vasculopathy, including vasculitis, coronary vasculitis, or arterial aneurysms (~11%)
  - Ocular inflammation, including severe treatment-resistant anterior uveitis, retinal vasculitis with chorioretinal scarring, and macular fibrosis (~9%)
  - Recurrent upper respiratory infections and/or lower respiratory infections (~9%)
  - Diabetes mellitus type 1 (~4%)
  - Autoimmune lymphoproliferative syndrome (1%)
  - Cardiac involvement, including pericardial effusion and/or pericarditis
  - Pulmonary nodules, pleuritis, and/or interstitial lung disease
  - Lupus nephritis and/or nephrotic syndrome
  - Secondary hemophagocytic lymphohistiocytosis and/or macrophage activation syndrome
  - Pernicious anemia
  - Hypogammaglobulinemia
  - Common variable immunodeficiency

Laboratory findings

- Elevated acute phase reactants (erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, serum ferritin concentration), especially during flares

  Note: These may be normal in individuals with findings that are more like an autoimmune disease and less like an autoinflammatory disease.

- Fluctuating or sustained presence of various autoantibodies (e.g., rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies, antithyroid antibodies, and antiplatelet antibodies); sometimes high titers

- Abnormal (reduced or elevated) leukocyte, neutrophil, or lymphocyte counts

- Reduced hemoglobin and/or platelet counts (especially during flares)
- Total immunoglobulins (IgG, IgM, IgA) can be elevated or reduced
- Reduced responses (i.e., antibody titers) to diphtheria and tetanus vaccinations
- Elevated transaminases (AST, ALT), especially during relapses
- Elevated fecal calprotectin
- Proteinuria or positive urine sediment (i.e., red blood cell / white blood cell casts)

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

Establishing the Diagnosis

The diagnosis of HA20 **is established** in an individual by identification of **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous *TNFAIP3* pathogenic (or likely pathogenic) variant (95% of affected individuals)
- A heterozygous deletion of 6q23 including *TNFAIP3* (<5% of affected individuals) [Franco-Jarava et al 2018, Shimizu et al 2021, Endo et al 2022, Elhani et al 2023]

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *TNFAIP3* variant of uncertain significance does not establish or exclude the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel), **chromosomal microarray analysis,** and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas comprehensive genomic testing does not.

- **A multigene panel for inborn errors of immunity, autoimmune lymphoproliferative syndrome, immunodeficiency, autoinflammation or periodic fever syndrome** that includes *TNFAIP3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TNFAIP3*) that cannot be detected by sequence analysis.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most used; **genome sequencing** is also possible. To date, the majority of reported *TNFAIP3* pathogenic variants (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Of note, several splicing variants beyond the canonical splice site have been identified [Kadowaki et al 2021, Similuk et al 2022].

  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 Haploinsufficiency of A20

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TNFAIP3	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~3% [4]
	CMA [6]	~2% [6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Based on Karri et al [2024] and data derived from 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TNFAIP3*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 6q23 region. CMA designs in current clinical use target the 6q23 region.
7. To date, a few deletions/duplications have been reported in individuals with haploinsufficiency of A20 [Franco-Jarava et al 2018, Tsuchida et al 2019, Shimizu et al 2021, Endo et al 2022].

Clinical Characteristics

Clinical Description

Haploinsufficiency of A20 (HA20), a complex immune dysregulation disease, is characterized by recurrent systemic immune dysfunction (inflammation and/or immune deficiency). HA20 demonstrates both variable expressivity (i.e., in an affected individual, different systems may be involved simultaneously and/or over time) and intrafamilial variability (i.e., variability in clinical presentation among affected individuals within the same immediate or extended family).

To date, more than 180 individuals from 97 families have been identified with HA20 [Elhani et al 2023, Karri et al 2024]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Haploinsufficiency of A20: Frequency of Select Rheumatologic Features

Feature	% of Persons w/Feature
Oral/genital ulcers	>70%

Table 2. continued from previous page.

Feature	% of Persons w/Feature
Recurrent fevers	49%
Skin rash	42%
Gastrointestinal disease	39%
Arthralgia/arthritis	34%
Lymphoproliferation	16%
Liver disease	15%
Neurologic disease	10%
Immunodeficiency	8%
Ocular inflammation	8%

Adapted with permission from Karri et al [2024]

Oral/genital ulcers, the most common manifestation of HA20, are recurrent and usually present during flares. Whereas oral ulcers are more common than genital ulcers and may be present in individuals who do not have genital ulcers, presence of genital ulcers in the absence of oral ulcers is less common. Both oral and genital ulcers can be quite painful and can cause scarring. Some individuals also may develop gastrointestinal ulcers. Although HA20 can mimic Behçet disease, affected individuals may have atypical features or not fully meet the international criteria for Behçet disease.

Recurrent fevers, present in many individuals, typically last for three to seven days and do not have a clear periodicity; however, there is variability between individuals. Rarely, recurrent febrile episodes can progress to cytokine storm and/or secondary hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS) [Elhani et al 2023, Karri et al 2024]. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are not always elevated.

Skin rash is highly variable and can include pustular rashes, folliculitis, vasculitic purpura, urticaria, and macular rashes. Up to 40% of individuals can develop an eczematoid dermatitis that does not always correlate with flares of disease activity [Schwartz et al 2021].

Gastrointestinal disease ranges from dull abdominal pain (caused by serositis, gastrointestinal ulcers, small bowel inflammation, or inflammatory colitis) to severe inflammation with risk of bowel perforation [Karri et al 2024]. Biopsies may resemble Crohn disease or may include nonspecific lymphoid aggregates.

Arthralgia/arthritis is most often relapsing and/or remitting nonerosive inflammatory polyarthritis with synovitis. Arthritis can be symmetric or asymmetric and may involve the axial joints. Although joint inflammation is usually nonerosive, in some individuals arthritis can be erosive and resemble psoriatic-like erosions or rheumatoid arthritis.

Lymphoproliferation most often presents as lymphadenopathy. Although affected individuals can rarely experience autoimmune lymphoproliferative syndrome-like disease (i.e., expansion of double-negative T cells and lymphoma), the exact link between these conditions and HA20 remains unclear.

Liver disease, including severe hepatitis, may be an underrecognized manifestation of HA20. If untreated, this can progress to cirrhosis and liver failure.

Neurologic disease. Central nervous system vasculitis/vasculopathy can manifest as severe headaches and cognitive changes; some individuals experience transient ischemic attacks. Other findings include aseptic meningitis, mononeuritis multiplex, chronic inflammatory demyelinating polyradiculoneuropathy, and/or peripheral neuropathy.

Hematologic involvement. Cytopenias can include pancytopenia, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune neutropenia, or lymphopenia. Leukocytosis and neutrophilia can also be seen.

Endocrine involvement. Both autoimmune thyroid disease and diabetes mellitus type 1 can be seen.

Less common findings in HA20 can include the following:

- **Kidney involvement.** Membranous nephropathy can resemble class V lupus nephritis with a "full house" (positive for IgA, IgG, IgM, C3, and C1Q) pattern of immunofluorescence.
- **Pericarditis and coronary vasculitis/vasculopathy**
- **Immunodeficiency,** most commonly recurrent infections that may also be diagnosed as common variable immunodeficiency. Five percent of individuals have had humoral deficiency (i.e., low IgG, IgA, IgM).
- **Ocular inflammation,** a rare manifestation, can present as uveitis, scleritis, episcleritis, and/or retinal vasculitis. Dry eye disease is also reported.
- **Lung inflammation** can include pulmonary nodules, pleuritis, or interstitial lung disease.
- **Other rare phenotypes** known to be associated with germline pathogenic variants in *TNFAIP3* (but not discussed in this *GeneReview*) include premature ovarian insufficiency, dental abnormalities, atrophic gastritis, and others. However, the association between some of these phenotypes and HA20 is not entirely clear. A full list of phenotypes described in association with A20 can be found in Elhani et al [2023] and Karri et al [2024].

Intrafamilial variability is considerable among family members who have the same *TNFAIP3* pathogenic variant; **interfamilial variability** is considerable among unrelated individuals who have the same *TNFAIP3* pathogenic variant.

Prognosis. With proper management the prognosis for HA20 is good; life expectancy is not expected to be significantly decreased. However, as with many monogenic complex immune deregulatory diseases, treatment is refractory and even fatalities have been reported [Elhani et al 2023].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified. While it appears that *TNFAIP3* pathogenic missense variants (compared to loss-of-function variants) might correlate with milder disease with reduced penetrance, more research is needed.

Penetrance

Most individuals with pathogenic variants in *TNFAIP3* have at least some manifestations of HA20. However, due to variable expressivity manifestations may go unrecognized or be subclinical.

Nomenclature

Because HA20 can mimic Behçet disease, it was originally identified as a monogenic Behçet disease (see Differential Diagnosis).

Prevalence

To date ~200 individuals with HA20 have been reported; however, prevalence is unknown.

Genetically Related (Allelic) Disorders

No monogenic conditions other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *TNFAIP3*.

Sporadic tumors, including B-cell lymphomas occurring as tumors in the absence of any other findings of haploinsufficiency of A20, frequently have a somatic inactivating pathogenic variant in *TNFAIP3* that is **not** present in the germline [Zhou et al 2016]. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Monogenic disorders of interest in the differential diagnosis of haploinsufficiency of A20 (HA20) are listed in Table 3.

Table 3. Monogenic Disorders of Interest in the Differential Diagnosis of Haploinsufficiency of A20

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/HA20	Distinguishing from HA20
ELF4	Familial Behçet-like autoinflammatory disease 2 (OMIM 301074)	XL	Early-onset autoinflammatory syndrome w/oral ulcers as most common feature & autoantibodies in some persons	Genital ulcers are not reported; may involve recurrent mucosal fungal infections.
OTULIN	Autoinflammation, panniculitis, & dermatosis syndrome (OMIM 615712)	AR	Diarrhea, leukocytosis, neutrophilia, & ↑ serum CRP	Otulipenia typically has more panniculitis & lipodystrophy
RELA	Familial Behçet-like autoinflammatory disease 3 (OMIM 618287)	AD	Characterized by oral & genital ulcers	Not assoc w/pathogenic autoantibodies &/or significant autoimmunity

AD = autosomal dominant; AR = autosomal recessive; CRP = C-reactive protein; HA20 = haploinsufficiency of A20; MOI = mode of inheritance; XL = X-linked

Trisomy 8-associated autoinflammatory disease (TRIAD). Similar to HA20, mosaic trisomy 8 is characterized by oral and genital ulcers along with fevers. The presence of dysmorphic features, platelet defects, and increased risk of hematologic malignancy in TRIAD distinguishes the disorder from HA20 [Lv et al 2024].

Acquired/polygenic disorders

- Behçet disease
- Systemic lupus erythematosus
- Juvenile idiopathic arthritis
- Aphthous stomatitis, pharyngitis, and adenitis
- Inflammatory bowel disease

Management

No clinical practice guidelines for haploinsufficiency of A20 (HA20) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with HA20 and similar disorders.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with HA20 (i.e., an individual with either a *TNFAIP3* pathogenic variant or a heterozygous deletion of 6q23 including *TNFAIP3*), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Haploinsufficiency of A20: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Rheumatologic	History & physical exam for signs/symptoms of systemic inflammation, fevers, serositis/pain, & joint involvement	Consider referral to rheumatologist to initiate biologic therapies (see Treatment of Manifestations).
	Assessment of inflammatory markers (serum CRP & ESR), CBC w/differential, & autoantibody titers (ANA, ANCA, CCP3, RF)	Imaging of abdomen to assess for splenomegaly &/or hepatomegaly should also be considered if there are findings of or suspected spleen or liver enlargement on physical exam.
Immunologic	Assessment for immune dysfunction or immunodeficiency	• Quantitative blood immunoglobulins (IgG, IgA, IgM) • Vaccine-specific responses (tetanus, diphtheria) • T/B/NK cell counts
Skin	Full skin exam	• To assess for rashes • Consider dermatology consultation for mgmt.
Eye	Ophthalmologic eval	For possible reduced vision, ptosis, abnormal eye movements, uveitis, retinal infarcts, &/or optic nerve damage
Kidney	Kidney function tests & urinalysis for proteinuria	If nephritis is suspected, consultation w/nephrologist is recommended.
	Consultation w/nephrologist	If there are signs/symptoms of renal involvement
Gastrointestinal	Fecal calprotectin to assess for inflammatory bowel disease	• Referral to gastroenterologist for endoscopy, enteroscopy, &/or colonoscopy • Can consider imaging (CT, ultrasound, MR enterography)
Liver	Transaminases (AST & ALT) & abdominal (liver) ultrasound	Referral to hepatologist if AST/ALT are elevated &/or liver ultrasound is abnormal
Cardiac	Consider echocardiogram to assess for pericarditis or cardiac involvement.	If coronary vasculitis/vasculopathy &/or AA amyloidosis are suspected, consider referral to cardiologist for noninvasive or direct angiography.
Hematologic	Hematologic eval	• When cytopenias are detected on CBC, perform bone marrow biopsy. • Assess for hemolysis, reticulocyte count. • Measure antiplatelet antibodies.
Endocrinologic	• Thyroid function tests • Assess for diabetes: obtain fasting blood glucose concentration & consider oral glucose tolerance test or hemoglobin A1c.	Consider endocrinologist referral if abnormal.
Neurologic	• Possible CNS involvement: consider MRI w/MRA & MRV (noninvasive angiography) or DSA (direct angiography) if CNS vasculitis is suspected. • Possible aseptic meningitis: lumbar puncture w/cell counts / protein / glucose concentration & bacterial/viral cultures • Possible peripheral nerve involvement: consider referral to neurologist for EMG &/or nerve biopsy if mononeuritis or vasculitic neuropathy is suspected.	• Consider referral to neurologist. • Diagnosis of vasculitic neuropathy requires treatment w/ escalating immunomodulators to prevent permanent nerve damage.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of HA20 to facilitate medical & personal decision making (e.g., predictive testing of at-risk family members; see Evaluation of Relatives at Risk).
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ALT = alanine transaminase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; AST = aspartate transaminase; CBC = complete blood count; CCP = cyclic citrullinated peptide; CNS = central nervous system; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; SAA = serum amyloid A

Treatment of Manifestations

There is no cure for HA20. In addition to use of a variety of biologic agents under the care of a rheumatologist, other supportive treatments can improve quality of life, maximize function, and reduce complications.

Biologic agents. Tumor necrosis factor (TNF) inhibitors, the most used medications for management of manifestations of HA20, directly target abnormal nuclear factor kappa B (NF-κB) signaling. Note: Affected individuals may have severe, paradoxical reactions associated with anti-TNF monoclonal antibodies.

In addition, interleukin-1 (IL-1) therapy and Janus kinase (JAK) inhibitors are effective in many individuals.

Corticosteroids, colchicine, methotrexate, azathioprine, thalidomide, mycophenolate, phosphodiesterase-4 inhibitors, and calcineurin inhibitors may also be useful. For more information on these medications from the American College of Rheumatology, see rheumatology.org/patients/treatments.

Hematopoietic stem cell transplantation (HSCT). In some instances of severe or refractory disease, HSCT may be considered. Family members considering stem cell donation should be tested for the family-specific *TNFAIP3* pathogenic variant.

Surveillance

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

- Rheumatologic features (see Table 2) should be monitored at least annually by a rheumatologist, and more frequently for individuals with evidence of systemic inflammation and/or organ involvement (typically including medical history, physical examination, and laboratory testing of acute phase reactants including CRP, ESR, fibrinogen, CBC with differential, SAA if available, and urinalysis for evidence of proteinuria).
- A low threshold for evaluation of subclinical inflammation by relevant subspecialists should be maintained:
  - Gastroenterologist for inflammatory bowel disease-like symptoms
  - Neurologist for aseptic meningitis
  - Ophthalmologist for symptoms of ocular inflammation
  - Endocrinologist for symptoms of thyroid disease, diabetes mellitus type 1
  - Nephrologist for manifestations of nephritis
  - Hematologist for manifestations of hematologic features
  - Neurologist for chronic inflammatory demyelinating polyradiculoneuropathy / encephalitis

- Immunologist for immunodeficiency
- Cardiologist for coronary vasculitis

Agents/Circumstances to Avoid

Vaccines. For individuals managed with continuous biologic agents, the American College of Rheumatology recommends against administration of live attenuated vaccines, unless medications can be paused for at least one dosing interval (typically 1-4 weeks) prior to AND following vaccination; however, shorter hold times can be considered if vaccination is critical [Bass et al 2023].

Note: Because many individuals with HA20 may not be able to tolerate prolonged cessation of continuous biologic therapy, risks/benefits should be considered before receiving any live vaccinations.

Evaluation of Relatives at Risk

For early diagnosis and treatment. 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 evaluation (see Evaluations Following Initial Diagnosis) and prompt initiation of treatment and/or surveillance.

For hematopoietic stem cell donation. When HSCT is considered, family members considering stem cell donation should be tested for the family-specific *TNFAIP3* pathogenic variant.

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

Pregnancy Management

Maternal medications should be discussed with a health care provider ideally prior to conception or as soon as a pregnancy has been recognized.

Information regarding adverse outcomes due to the use of TNF inhibitors in human pregnancy is limited; to date, no pattern of birth anomalies with any of the TNF inhibitor medications has been reported. Per the American College of Rheumatology guidelines [Sammaritano et al 2020], the use of anti-TNF agents in rheumatic diseases is recommended for women with active disease, with consideration of weaning such medication during the third trimester to decrease placental transfer to the fetus if maternal remission has been achieved. However, as with any medication treatment during pregnancy, discussion of the risks versus benefits of such treatment between the affected individual and their health care provider is encouraged [De Felice & Kane 2021].

Information regarding the safety of the use of IL-1 inhibitors in human pregnancy is limited; to date, no pattern of birth anomalies in humans have been reported with IL-1 or IL-1R inhibitor medication classes. These medications are often continued during pregnancy; it is recommended that clinicians discuss risks and benefits with affected individuals.

Colchicine, azathioprine, and hydroxychloroquine are generally continued during pregnancy; however, it is recommended that clinicians discuss risks and benefits with affected individuals.

Mycophenolate, methotrexate, and thalidomide are all known human teratogens and should be avoided during pregnancy. Less information is available for JAK inhibitors, although these are generally also avoided during pregnancy due to concerns about potential embryo disruption in animal models.

The use of corticosteroids during human pregnancy has been associated with an increased risk of cleft lip with or without cleft palate and growth restriction in exposed fetuses; however, the risks and benefits of treatment should be weighed carefully, as uncontrolled inflammation may also have risks [Odufalu et al 2022].

See MotherToBaby for further information on medication use during pregnancy.

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

Haploinsufficiency of A20 (HA20) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with HA20 have an affected parent.
- Some individuals diagnosed with HA20 have the disorder as the result of a *de novo* *TNFAIP3* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment. Note: A proband may appear to be the only affected family member because of failure to recognize the disorder in family members, intrafamilial variability, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, *de novo* occurrence of a *TNFAIP3* pathogenic variant in the proband cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the *TNFAIP3* pathogenic variant.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

      * A parent with somatic and gonadal mosaicism for a *TNFAIP3* pathogenic variant may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Intrafamilial variability is

considerable among family members who have the same *TNFAIP3* pathogenic variant; affected family members may have different disease manifestations and severity.
- If the *TNFAIP3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *TNFAIP3* pathogenic variant but appear to be clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for HA20 because of the possibility of reduced penetrance or variable expressivity (manifestations may go unrecognized or be subclinical) in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with HA20 has a 50% chance of inheriting the *TNFAIP3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *TNFAIP3* pathogenic variant, the parent's family members may be at risk.

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.

Predictive testing for at-risk asymptomatic family members requires prior identification of the germline *TNFAIP3* pathogenic variant in the family.

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TNFAIP3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Autoinflammatory Alliance**
  Email: karen@autoinflammatory.org
  autoinflammatory.org
- **Eurofever Project**
  printo.it/eurofever/index

- **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
  Phone: 877-226-4267
  Email: niamsinfo@mail.nih.gov
  niams.nih.gov
- **Eurofever Registry**
  Paediatric Rheumatology International Trials Organisation (PRINTO)
  Italy
  Phone: +39 010 382854; +39 010 393425
  Fax: +39 010 393324; +39 010 4211018
  Email: marcogattorno@gaslini.org; printo@gaslini.org
  Eurofever Project - The Eurofever registry

Molecular Genetics

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

Table A. Haploinsufficiency of A20: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TNFAIP3	6q23.3	Tumor necrosis factor alpha-induced protein 3	TNFAIP3 @ LOVD	TNFAIP3	TNFAIP3

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 Haploinsufficiency of A20 (View All in OMIM)

191163	TUMOR NECROSIS FACTOR-ALPHA-INDUCED PROTEIN 3; TNFAIP3
616744	AUTOINFLAMMATORY SYNDROME, FAMILIAL, BEHCET-LIKE 1; AIFBL1

Molecular Pathogenesis

TNFAIP3 encodes tumor necrosis factor alpha-induced protein 3 (TNFAIP3; also known as A20), which regulates signaling pathways critical for inflammation, proliferation, and cellular homeostasis including TNF, NF-κB, necroptosis, inflammasome activation, JNK signaling, and JAK-STAT signaling.

Mechanism of disease causation. Haploinsufficiency

***TNFAIP3*-specific laboratory technical considerations.** The majority of *TNFAIP3* pathogenic variants are frameshift, nonsense, or splice-site variants or deletions.

Although a few missense variants have been described, their segregation in families is not clear, leading to speculation that they may be associated with milder disease.

Missense variants should be evaluated with functional assays to confirm pathogenicity [El Khouri et al 2023]. Such assays may include ectopic overexpression of wild type vs mutated A20 in cell lines and measurement of TNF-induced NF-κB activation, or measurement of A20 expression in patient cells and mutation-negative controls (preferably family controls) [Zhou et al 2016, Kadowaki et al 2021].

Chapter Notes

Author Notes

Daniella M Schwartz (daniella.schwartz@pitt.edu) is actively involved in the treatment of and clinical research regarding individuals with haploinsufficiency of A20 (HA20). She would be happy to communicate with persons who have any questions regarding diagnosis or treatment of HA20 or other considerations.

Natalie Deuitch (natalie.deuitch@nih.gov) and Ivona Aksentijevich (aksentii@arb.niams.nih.gov) are also interested in hearing from clinicians treating families affected by autoinflammatory disorders in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact any of the authors to inquire about review of *TNFAIP3* variants of uncertain significance.

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