

See below for Additional Technical Information topics

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Antibody, IgG Idiopathic Inflammatory Myopathies (Myositis)

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Antibody, IgG

Indications for Ordering

- Differential diagnosis of myositis in patients with or without statin exposure
- Monitor response to treatment

Test Description

Semiquantitative enzyme-linked immunosorbent assay

Tests to Consider

Primary test

[3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase \(HMGCR\) Antibody, IgG 2013101](#)

- Detects IgG autoantibodies against HMGCR
- In addition to clinical evaluation for muscle strength and serum creatine kinase, may be useful to monitor response to treatment

Related tests

[Creatine Kinase, Total, Serum or Plasma 0020010](#)

- Nonspecific indicator of muscle inflammation or damage
- Monitor therapeutic response

[Myositis Extended Panel 2013961](#)

- May be useful for differential evaluation of polymyositis, dermatomyositis, necrotizing autoimmune myopathy, or overlap syndromes associated with connective tissue disease

[Polymyositis and Dermatomyositis Panel 2013992](#)

- May be useful for evaluation of patients with progressive proximal muscle weakness and/or with cutaneous manifestations suggestive of dermatomyositis and/or associated connective tissue disease

[Anti-Nuclear Antibody \(ANA\), IgG by IFA with Reflex by IFA Pattern 2008467](#)

- Initial screen for autoimmune connective tissue diseases

[Connective Tissue Diseases Profile 0051668](#)

- Confirmatory tests for specific connective tissue disease

[Statin Sensitivity *SLCO1B1*, 1 Variant 2008426](#)

- Identify individuals at increased risk for statin-related muscle toxicity

Disease Overview

Age of onset – 30-70 years

Most common clinical features

- Persistent and progressive proximal weakness
- Myalgia
- Elevated serum creatine kinase concentration
 - >10,000 IU/L mean concentration prior to treatment
 - Range – 950-45,000 IU/L

Physiology

- Presence of anti-HMGCR antibodies is associated with a rare form of idiopathic inflammatory myopathy referred to as necrotizing autoimmune myopathy
- Anti-HMGCR IgG antibodies are mainly associated with exposure to statins
 - Also occur in statin-naïve patients with myositis
- Muscle biopsy is associated with
 - Abundant necrotic fibers
 - Sparse lymphocytic infiltrate
 - Complement deposits on capillaries
 - Increased expression of major histocompatibility complex class 1 molecules
- In most patients, statin-induced myopathy resolves within months after discontinuation of treatment
 - Minority develop a progressive necrotizing myopathy associated with anti-HMGCR antibodies
 - Requires immunosuppressive therapy
- Response to treatment is associated with
 - Decline in antibody titers and creatine concentration
 - Improvement in muscle strength

Test Interpretation

Sensitivity/specificity

- Analytical sensitivity – 94.4% (Hamann, 2013)
- Analytical specificity – 99.3% (Hamann, 2013)

Results

- Positive – ≥ 20 units
- Negative – < 20 units

Limitations

- Diagnostic relevance in a minor subset of patients with inflammatory myopathy
- Results should be used in conjunction with clinical findings, muscle biopsy, and other relevant laboratory tests for disease evaluation
- Negative results do not rule out inflammatory myopathy, necrotizing autoimmune myopathy, or statin-associated myopathy

References

- Christopher-Stine L, Casciola-Rosen LA, et al. A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. *Arthritis Rheum.* 2010;62:2757-2766

- Hamann P, Cooper R, et al. Statin-induced necrotizing myositis – a discrete autoimmune entity within the “statin-induced myopathy spectrum.” *Autoimmun Rev.* 2013;12(12):1177-1181
- Mammen AL, Chung T, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum.* 2011;63:713-721
- Mammen AL, Gaudet D, et al. Increased frequency of DRB1*11:01 in anti-hydroxymethylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Arthritis Care Res.* 2012;64:1233-1237
- Werner JL, Christopher-Stine L, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Arthritis Rheum.* 2012;64:4087-4093

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Idiopathic Inflammatory Myopathies (Myositis)

Indications for Ordering

Differential diagnosis of inflammatory myopathies in conjunction with muscle biopsy and clinical presentation

Test Description

Polymyositis and Dermatomyositis Panel

Myositis Extended Panel

- Qualitative immunoprecipitation/semiquantitative multiplex bead assay/qualitative immunoblot

Polymyositis Panel

- Qualitative immunoprecipitation/semiquantitative multiplex bead assay

Dermatomyositis Panel

- Qualitative immunoprecipitation/qualitative immunoblot

Interstitial Lung Disease Panel

- Qualitative immunoprecipitation/semiquantitative multiplex bead assay/qualitative immunoblot/semiquantitative enzyme-linked immunosorbent assay/quantitative immunoturbidimetry

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) Antibody, IgG

- Semiquantitative enzyme-linked immunosorbent assay

Tests to Consider

Typical testing strategy

Initial screening tests

- Creatine kinase
- Erythrocyte sedimentation rate/C-reactive protein
- Thyroid-stimulating hormone – rule out thyroid disease as etiology for myopathy
- Metabolic profile

- Complete blood count
- Antinuclear antibodies

Antibody testing (minimum recommended)

- Antisynthetase antibodies – anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ
- Nonsynthetase antibodies – anti-Mi2, anti-p155/140, anti-SRP
- Myositis associated antibodies – anti-PM/Sci-100, anti-SSA(RO), anti-U1 RNP

Definitive diagnosis

- Muscle biopsy (which can be guided by MRI) is gold standard

Primary tests

[Polymyositis and Dermatomyositis Panel 2013992](#)

- May be useful for evaluation of patients with progressive proximal muscle weakness and/or with cutaneous manifestations suggestive of dermatomyositis and/or associated connective tissue disease
- Components
 - Jo-1 antibody, IgG
 - PL-7 (threonyl-tRNA synthetase) antibody
 - PL-12 (alanyl-tRNA synthetase) antibody
 - EJ (glycyl-tRNA synthetase) antibody
 - SRP (signal recognition particle) antibody
 - OJ (isoleucyl-tRNA synthetase) antibody
 - Mi-2 (nuclear helicase protein) antibody
 - P155/140 antibody
 - SAE1 (SUMO activating enzyme) antibody
 - MDA5 (CADM-140) antibody
 - NXP-2 (nuclear matrix protein-2) antibody
 - TIF1-gamma (TIF1-y) antibody

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[Myositis Extended Panel 2013961](#)

- May be useful for differential evaluation of polymyositis, dermatomyositis, necrotizing autoimmune myopathy, or overlap syndromes associated with connective tissue disease
- Components
 - SSA 52 and 60 (Ro) (ENA) antibodies, IgG
 - RNP (U1) (ribonucleic protein) (ENA) antibody, IgG
 - Jo-1 antibody, IgG
 - Mi-2 (nuclear helicase protein) antibody
 - PL-7 (threonyl-tRNA synthetase) antibody
 - PL-12 (alanyl-tRNA synthetase) antibody
 - P155/140 (TIF1-gamma) antibody
 - EJ (glycyl-tRNA synthetase) antibody
 - Ku antibody
 - U2 sn (small nuclear) RNP antibody
 - SRP (signal recognition particle) antibody
 - OJ (isoleucyl-tRNA synthetase) antibody
 - SAE1 (SUMO activating enzyme) antibody
 - MDA5 (CADM-140) antibody
 - NXP-2 (nuclear matrix protein-2) antibody
 - TIF1-gamma (TIF1-γ) antibody
 - Fibrillarin (U3 RNP) antibody, IgG
 - PM/Scl-100 antibody, IgG by Immunoblot

[Polymyositis Panel 2013990](#)

- May be useful for evaluation of patients with progressive proximal muscle weakness and antisynthetase syndrome
- Components
 - Jo-1 antibody, IgG
 - PL-7 (threonyl-tRNA synthetase) antibody
 - PL-12 (alanyl-tRNA synthetase) antibody
 - EJ (glycyl-tRNA synthetase) antibody
 - SRP (signal recognition particle) antibody
 - OJ (isoleucyl-tRNA synthetase) antibody

[Dermatomyositis Panel 2013991](#)

- May be useful for evaluation of patients with characteristic cutaneous manifestations of dermatomyositis with or without muscle weakness
- Components
 - Mi-2 (nuclear helicase protein) antibody
 - P155/140 (TIF1-gamma) antibody
 - SAE1 (SUMO activating enzyme) antibody
 - MDA5 (CADM-140) antibody
 - NXP-2 (nuclear matrix protein-2) antibody
 - TIF1-gamma antibody

[Interstitial Lung Disease Panel 2013993](#)

- May be useful for evaluation of interstitial lung disease in the context of connective tissue disease
- Components
 - SSA 52 and 60 (Ro) (ENA) antibodies, IgG
 - Scleroderma (Scl-70) (ENA) antibody
 - Jo-1 antibody, IgG
 - PL-7 (threonyl-tRNA synthetase) antibody
 - PL-12 (alanyl-tRNA synthetase) antibody
 - EJ (glycyl-tRNA synthetase) antibody
 - Ku antibody
 - SRP (signal recognition particle) antibody

- OJ (isoleucyl-tRNA synthetase) antibody
- PM/Scl-100 antibody, IgG by immunoblot
- MDA5 (CADM-140) antibody
- NXP-2 (nuclear matrix protein-2 Ab)
- Rheumatoid factor
- Cyclic citrullinated peptide (CCP) antibody, IgG
- Nuclear antibody (ANA) by IFA, IgG

[3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase \(HMGR\) Antibody, IgG 2013101](#)

- Differential diagnosis of myositis in patients with or without statin exposure
- In addition to clinical evaluation for muscle strength and serum creatine kinase, may be useful to monitor response to treatment

Related tests

- [Creatine Kinase, Total, Serum or Plasma 0020010](#)
- [Anti-Nuclear Antibodies \(ANA\), IgG by ELISA with Reflex to ANA, IgG by IFA 0050080](#)
- [SSA 52 and 60 \(Ro\) \(ENA\) Antibodies, IgG 2012074](#)
- [Jo-1 Antibody, IgG 0099592](#)
- [RNP \(U1\) \(Ribonucleic Protein\) \(ENA\) Antibody, IgG 0050470](#)
- [Signal Recognition Particle \(SRP\) Antibody 2002098](#)
- [PM/Scl-100 Antibody, IgG by Immunoblot 2003040](#)
- [Fibrillarin \(U3 RNP\) Antibody, IgG 2012173](#)

Disease Overview

Incidence – 4-10/million adults; rare in children

Age of onset – varies by disorder

- Dermatomyositis (DM)
 - Bimodal – childhood and 50-70 years
- Polymyositis (PM) – rare in childhood, typically >20 years
- Inclusion body myositis (IBM) – >50 years
- Necrotizing autoimmune myositis – primarily adults, often older

Syndromes

- DM – associated with cancer
- PM
- IBM
- Necrotizing autoimmune myositis
- Overlap syndrome
- Juvenile DM and PM

Symptoms

General features

- Musculoskeletal – progressive muscle weakness (usually symmetrical and proximal)
 - Pharyngeal and neck flexion muscles frequently involved
- Arthralgias/arthritis – wrists, knees, small joints of hands
- Constitutional – fever, weight loss
- Pulmonary – fibrosing alveolitis, aspiration pneumonia
- Gastrointestinal – esophageal dysfunction, dysphagia
- Cardiovascular – myo-/pericarditis, valvular disease, rhythm disturbances
- Renal – rarely myoglobinuria, glomerulonephritis

- Dermatologic – Raynaud phenomenon, rashes, calcinosis over bony prominences

Antisynthetase syndrome

- Found almost exclusively in middle-aged women with DM or PM
- Characterized by
 - Low-grade fevers
 - Interstitial pneumonitis – major determinant of morbidity and mortality
 - Hyperkeratosis, cracking of lateral and palmar aspects of the fingers (mechanic’s hands)
 - Raynaud phenomenon
 - Inflammatory polyarthritis, myalgias
- Presence of antinuclear antibodies known as antisynthetases

DM

- Characteristic photosensitive rash accompanied by symmetrical, subacute, proximal muscle weakness
 - Rash usually precedes muscle symptoms
 - Blue-purple rash – symmetrical distribution
 - Violaceous discoloration of upper eyelids with periorbital edema (heliotrope rash)
 - Erythema of metacarpophalangeal proximal and distal joints
 - Raised violaceous rash (Gottron sign) or scaly erythematous plaques over dorsal surface of bony prominences (Gottron papules) – considered pathognomonic for DM
 - Macular erythema over the lower neck and upper chest in a V-distribution (V-sign), over upper back (Shawl sign), or over upper thighs (Holster sign)
 - Telangiectasias at base of fingernails, cuticular overgrowth and periungual erythema
 - Vasculitic skin changes
 - Subcutaneous nodules, periungual infarcts, digital ulcerations
- Cancer-associated myositis
 - Most commonly associated with DM, but can be found in PM
 - May be diagnosed prior to, simultaneously with, or after myopathy
 - Increased risk of malignancy (20-25%) of any of the following types (highest risk in first 2-3 years after diagnosis)
 - Ovarian
 - Breast
 - Melanoma
 - Colorectal
 - Non-Hodgkin lymphoma
- Amyopathic DM
 - Characteristic cutaneous findings of DM >6 months without muscle involvement
 - May progress to DM
 - Some risk for lung disease, malignancy
 - Electromyography may demonstrate subtle myopathy

PM

- Dominated by muscular presentation
 - No rash
- Usually subacute presentation
- May be associated with other autoimmune diseases
- Diagnosis of exclusion – must rule out the following
 - Neuromuscular disease
 - Endocrinopathy
 - Muscular dystrophy
 - Known biochemical muscle disorder or familial biochemical disorder
 - Drug-induced myopathy

IBM

- Two types – sporadic, hereditary
- Muscle involvement
 - Muscle atrophy early in disease
 - Distal weakness is most common – deep finger flexors and foot extensors common
 - Asymmetric distribution is common
 - Proximal muscles less frequently involved
 - Specific muscles
 - Small muscles in hand frequently involved
 - Quadriceps involvement common – associated with frequent falls
 - Facial muscles frequently involved
- Extramuscular disease rare – dysphagia is the exception (>50% of patients)
- May be misdiagnosed as PM, adult-onset muscular dystrophy, or motor neuron disease
- Associated with other autoimmune diseases

Necrotizing autoimmune myositis

- Acute or subacute presentation
- Severe proximal muscle weakness – clinically indistinguishable from PM
- May occur in association with cancer, other CT diseases, or drug use (eg, statins)
- Diagnosis of exclusion

Overlap syndrome

- Most common in DM but can occur with other inflammatory myopathies
- Myositis in conjunction with connective tissue disease
 - Most common – systemic sclerosis, mixed connective tissue disease, systemic lupus erythematosus
- Rash – faint or transient
- Frequent association with antisynthetase antibodies
- Myopathy varies from mild to dominant presentation

Juvenile disease

Juvenile dermatomyositis (JDM)

- ~85% of juvenile idiopathic inflammatory myopathy (JIIM)
- Symmetrical and proximal muscle weakness
- Gottron papules
- Heliotrope rash
- Periungual telangiectasia
- Vasculitis – more common than in adults
- Other organs
 - Cardiac
 - Joints
 - Gastrointestinal
 - Pulmonary
- May have family history of other autoimmune diseases
- Amyopathic (hypomyopathic form)
 - Inflammatory rashes without muscle weakness
 - ~25% develop full-blown dermatomyositis

Juvenile polymyositis

- 4-8%
- Proximal and distal muscle weakness
- Frequent falling episodes
- Cardiac damage

Juvenile connective tissue disease myositis

- 6-11% of JIIM
- Occurs in conjunction with another connective tissue disease
- Raynaud phenomenon
- Arthritis
- Malar rash
- Interstitial lung disease

Diagnostic issues

May be difficult to distinguish between myopathies

- Antibody testing in conjunction with clinical presentation and muscle biopsy help to confirm the diagnosis
- Distinction may be important for therapy and prognosis

Antibody testing

- Myositis-specific antibodies
 - Antisynthetase antibodies
 - Anti-Jo-1 (histidyl-tRNA synthetase) – more common in polymyositis
 - Anti-PL7 (threonyl-tRNA synthetase)
 - Anti-PL-12 antibodies (anti-alanyl-tRNA synthetase)
 - Anti-EJ (glycyl-ts RNA synthetase)
 - Anti-OJ (anti-isoleucyl-tRNA synthetase)
 - Anti-KS (asparaginyl tRNA synthetase)
 - Anti-Ha (tyrosyl tRNA synthetase)
 - Anti-Zo (phenylalanyl tRNA synthetase)

○ Nonsynthetase antibodies

- Anti-signal recognition particle (anti-SRP)
 - Necrotizing myopathy
 - Severe cardiac involvement
- Anti-p155/140
 - JDM, DM, and ulceration
 - Adults – DM, increased malignancy risk
- Anti-Mi-2
 - DM
 - Not associated with increased malignancy risk
 - Steroid responsiveness
- Anti-CADM-140
 - CADM
 - Rapidly progressive ILD
- Anti-p140
 - JDM, DM, and calcinosis
 - Adults – DM, increased malignancy risk, ILD
- Anti-SAE
 - DM
- Anti-HMGCR
 - Necrotizing myopathy
- Response to short-term statin withdrawal
- Myositis-associated antibodies – usually associated with connective tissue disease/overlap syndrome
 - Anti-PM-Scl – polymyositis-scleroderma
 - Anti-U1 RNP
 - Anti-Ku
 - Anti-Ro (SSA)

Test Interpretation

Results

- Positive – as a single test, not diagnostic for inflammatory myopathy
- Negative – does not rule out inflammatory myopathy

Limitations

- Results by themselves are not diagnostic; strong clinical correlation is recommended
- Negative results do not rule out a diagnosis of inflammatory myopathy or overlap syndrome