

## Chapter 2

# Classification of Idiopathic Inflammatory Myopathies

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**Abstract** Although it has been long recognized that inflammatory muscle disease of unknown etiology may present clinically and respond to therapy in a variety of ways, our approaches regarding how to best classify or divide these entities into more understandable groups of patients has evolved as larger series have been studied using advanced laboratory, immunopathologic, and genetic technologies. In addition to the traditional clinicopathologic classifications of these entities, there is increasing interest in using newer methods, including serology, environmental exposures, and molecular genetics, to divide these syndromes into more homogeneous subsets. While our understanding of these disorders is far from complete, it is clear that the inflammatory myopathies are composed of many separate and distinct disorders with widely divergent clinical signs, symptoms, pathology, laboratory abnormalities, immune responses, genetic and environmental risk factors, and prognoses. Classification of the inflammatory myopathies remains unsatisfactory and controversial, with a number of competing approaches currently in use. Nonetheless, while many different schemes have been proposed, this chapter focuses on the classifications based on clinical signs, pathology, and autoantibodies that today are useful in assessing subjects, as well as possible new approaches that take into account environmental exposures and immunogenetics. Our understanding of the pathogenesis, classification, and prognosis of the inflammatory myopathies will become more complete as we decipher the interrelationships among all the critical features of disease—including the genetic and environmental risk factors necessary and sufficient for the induction of myositis—and develop more rational ways of dividing and treating these increasingly recognized syndromes.

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## Defining the Idiopathic Inflammatory Myopathies

It is often difficult to define rare forms of disease whose pathogeneses remain obscure, and the idiopathic inflammatory myopathies (IIMs) are no exception. A primary problem is that sharp boundaries do not exist among many of the syndromes that result in muscle weakness, and none of the multiple competing current diagnostic criteria is able to divide reliably all IIM cases from the many dystrophic, metabolic, infectious, and other causes of myopathy (1). Whatever classification criteria are used, a significant number of patients seen in referral centers still defy diagnosis, and empiric therapies are often required. Also, because different specialists tend to use different ways to identify and evaluate myositis patients, it remains difficult to integrate the literature in the field regarding the clinical utility of different classification schemes. Furthermore, the systemic nature of many of these disorders and the resulting cutaneous, cardiac, pulmonary, and gastrointestinal manifestations can confuse the presentation and result in misdiagnosis and delayed therapy.

While imperfect, the criteria for the diagnosis of polymyositis (PM) and dermatomyositis (DM) proposed by Bohan and Peter (2) over 30 years ago remain useful today with certain modifications. Due to the limitations inherent in the Bohan and Peter criteria, a group of specialists interested in standardizing the assessment and study of IIMs, the International Myositis Assessment and Clinical Studies Group, or IMACS, has revised these criteria to include the need for a muscle biopsy consistent with the diagnosis of PM and the need for the presence of specific rashes to define DM (3). Thus, after rigorously excluding the many other causes of myopathy, the presence of the following criteria usually establishes a diagnosis: for PM, the finding of proximal muscle weakness, elevated serum levels of sarcoplasmic enzymes, myopathic changes on electromyography, and a muscle biopsy showing myofiber degeneration and regeneration with chronic inflammatory infiltrates; in the case of DM, the presence of the heliotrope rash or Gottron's papules. The diagnosis of inclusion body myositis (IBM) was accepted by IMACS as that defined by Greggs et al. (4).

Some groups have proposed that using the Bohan and Peter criteria (2) will over- or misdiagnose these conditions and proposed alternative pathologic approaches (5). However, given the limited data available today, it remains unclear if use of these alternative approaches will actually improve patient therapies or outcomes (6). Nonetheless, it is clear that even the IMACS-modified Bohan and Peter criteria have limitations, and it is useful to consider additional clues that can lead to the diagnosis of IIM in unclear cases. These include the presence of certain autoantibodies, a family history of autoimmunity, other signs of connective tissue disease in the patient, symmetric inflammatory changes on magnetic resonance imaging of muscle, and a clinical

response to immunosuppressive therapy (7). In fact, it has been clear for some time that new criteria are needed to define the IIMs and to subclassify them; a large international study is now ongoing to accomplish these tasks (see <http://www.niehs.nih.gov/research/resources/collab/imacs/classificationcriteria.cfm>). Until the pathogenetic mechanisms of these disorders are defined and the distinctions among the types of IIMs substantiated, these syndromes will remain diagnoses of exclusion and heterogeneous complexes of clinical signs, symptoms, and laboratory findings that fulfill the criteria discussed rather than unique disorders. It is hoped that the deficiencies in the current classifications will become clearer as we understand the interrelationships of the many features of the different forms of myositis. Many new biomarker technologies, including advances in genetics, proteomics, and gene expression arrays, will also surely have an impact in assisting in the future diagnosis and classification of myositis.

## Clinicopathologic Classifications

Since clinical and histopathologic features are what physicians focus on in the evaluation of patients with muscle weakness or elevated creatine kinase (CK) activity and because these features have been useful in defining different groups of myositis patients in terms of severity of disease, responses to therapy, and prognoses, the major classification schemes are based on these elements. As is the case with all forms of classification, however, there remains disagreement in the field regarding the appropriate ways of applying clinicopathologic features to divide the myositis syndromes. A modification of several previously proposed clinicopathologic classifications is listed in Table 2.1. Unfortunately, these categories are not all mutually exclusive. For example, juvenile myositis patients may also be categorized as having PM, DM, myositis in association with another connective tissue disease (overlap myositis), or even rarely cancer-associated myositis (CAM), or IBM. It remains unclear which of these diagnostic divisions is more important because no study has had adequate numbers of patients within these many categories to address this question appropriately in a multivariate analysis. Certain entities (e.g., focal or nodular myositis, myositis ossificans, and macrophagic myofasciitis) have been included in this discussion because they may develop as a result of distinct etiologic mechanisms; however, definite clinicopathologic differences have yet to be documented among all these disorders.

Many lines of evidence suggest that primary idiopathic PM differs from primary idiopathic DM. Support includes differences in clinical presentation, histopathology, the number and distribution of both circulating and muscle-infiltrating CD4<sup>+</sup> and CD8<sup>+</sup> T cells and B cells, responses to therapy, different environmental exposures, and genetics (reviewed in (7)). Controversy continues regarding whether a distinct entity known as DM without myositis (*dermatomyositis sine myositis*) exists or if this is simply one end of a spectrum of disease severity (8).

**Table 2.1** A clinicopathologic classification of the idiopathic inflammatory myopathies<sup>a</sup>

Clinicopathologic category	Associations and comments
Polymyositis	A diagnosis of exclusion: defined by the absence of all the features below in a patient meeting IIM criteria; muscle biopsy often shows endomysial infiltration of myocytes, primarily by CD8 <sup>+</sup> T cells
Dermatomyositis	Heliotrope rash or Gottron's papules are pathognomonic, but other rashes may be present; myositis may be clinically absent but can be seen by biopsy or magnetic resonance imaging (MRI); muscle biopsy often shows perifascicular atrophy, microvascular changes, and deposits of the membrane attack complex and prominent perivascular CD4 <sup>+</sup> T cells and B cells
Myositis associated with another connective tissue disease	Mild myositis, good response to therapy; rheumatoid arthritis, systemic sclerosis, and lupus are most common as overlaps
Juvenile myositis	Age of onset <18 years, frequent calcifications, occasional gastrointestinal vasculitis; better responses to therapy and outcomes than adult forms
Cancer-associated myositis	Myositis onset often within 2 years of the diagnosis of cancer; different cancers may be overrepresented in polymyositis (PM) and dermatomyositis (DM)
Inclusion body myositis	Occurs mainly in older white men with insidious onset and progression and poor response to therapy; asymmetric distal weakness with wrist and index finger flexors weaker than extensors; rimmed vacuoles and amyloid found in myofibers with characteristic tubulofilaments on ultrastructural analysis
Granulomatous myositis	Granulomas prominent in muscle biopsy; can be seen in sarcoidosis
Eosinophilic myositis	Eosinophils prominent in muscle; can be a part of hypereosinophilic syndrome or eosinophilic fasciitis
Vasculitic myositis	Vasculitis prominent in muscle; can be part of other vasculitides, including polyarteritis nodosa
Orbital or ocular myositis	Involvement of extraocular muscles only; periorbital pain, proptosis, and diplopia; diagnosis confirmed by ultrasound, computed tomography (CT), or MRI
Focal or nodular myositis	Focal involvement of one or more limbs; can progress to polymyositis, remain isolated, or resolve
Myositis ossificans	Occurs as a local limited phenomenon or more generalized excessive proliferation of connective tissue and replacement by bone
Macrophagic myofasciitis	Persistent fatigue, localized then diffuse myalgia mostly in lower limbs with little or no loss of muscle strength and no muscle wasting; biopsy shows perifascicular cellular infiltrate of clusters of macrophages with occasional CD8 <sup>+</sup> lymphocytes and intact muscle fibers; in most cases develops after immunization with aluminum hydroxide-containing vaccines

<sup>a</sup>Modified from (53); information derived from (3,4,7,11,18,22,54,55); categories are not mutually exclusive

Difficulties in assessing whether a classification scheme should include this as a separate category relate to the frequent delay between the development of the rash and muscle involvement in DM, the relatively mild muscle weakness and lower serum CK levels in DM, and the understandable reluctance of physicians to perform muscle biopsy or electromyography to confirm muscle disease in a patient without clinical evidence of weakness. Magnetic resonance imaging and histopathologic studies suggest that there are alterations in the muscles of at least some patients who have Gottron's papules or heliotrope rash but do not have clinical evidence of muscle weakness.

The category known as overlap myositis has been proposed to occur when a subject meets PM/DM or IBM criteria and criteria for another connective tissue disease, such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, or Sjogren's syndrome (9). Other researchers, however, have more recently defined this group in other ways on the basis of the presence of certain autoantibodies (10). Using the original definition, connective tissue disease overlap myositis (CTM) appears to differ from primary PM or DM in several ways. CTM tends to be characterized by different frequencies of certain clinical signs and symptoms, different frequencies and types of autoantibodies, possible histopathologic differences, and a less-severe myositis with a better response to therapy (9).

As mentioned, our recognition of the diversity of clinical, serologic, and pathologic presentations of juvenile myositis is increasing, and there may be fewer differences from the adult forms of myositis than previously believed. Nonetheless, juvenile myositis patients tend to have a higher frequency of vasculitic complications and soft tissue calcifications and a better response to therapy than that seen in most adult myositis patients (11–13).

Cancer-associated myositis has been controversial, although early anecdotes and later epidemiologic data suggested that PM, DM, and IBM patients have an increased risk of a variety of cancers, with most, but not all, cancers diagnosed within 2 years of the onset of myositis (14,15). Since DM appears to respond in some cases to simple resection of the associated cancer and because a return of the rash can herald the reappearance of the cancer, it seems likely that the development of the myositis is closely linked either to factors generated by the neoplastic cells or to immune responses to the malignant cells. Although any cancer can occur in myositis patients, certain ones may be more common. In DM, ovarian, lung, pancreatic, stomach, and colorectal cancers, and non-Hodgkin lymphoma were significantly increased in a study in Scandinavia (15). In contrast, PM was associated with a raised risk of non-Hodgkin lymphoma and lung and bladder cancers. CAM patients have a poorer prognosis as a result of their cancer compared to other myositis patients. Features that are statistically less likely to be associated with CAM include myositis-specific and -associated autoantibodies and interstitial lung disease (9,16).

The different clinical, serologic, prognostic, and pathologic features of IBM certainly justify a separate category for this entity, but recent information suggests the line between PM and IBM may not be so clear, and intermediate forms may be more common than generally appreciated (17). The variants of eosinophilic, granulomatous, and vasculitic myositis have distinctive muscle pathology features as

well (18), and they are also likely to have different pathogenetic mechanisms; their rarity, however, has not allowed a careful documentation of clinical differences from the other forms of IIMs.

A number of rare and unusual IIMs have also been described that are focal in nature and are not systemic disorders and thus are not typically considered IIMs (19). One form, called ocular or orbital myositis, involves chronic inflammation of structures within the orbit. Ocular or orbital myositis often begins with unilateral periorbital pain usually made worse with eye movement, proptosis, diplopia, and swelling of the eyelid. The diagnosis is often made by orbital ultrasonography, high-resolution computerized tomography, or magnetic resonance imaging. Another group of exceedingly rare syndromes is defined by local areas of pain, swelling, or weakness and on biopsy shows the typical features of inflammatory myopathy. These cases have been called variously focal, nodular, or focal nodular myositis (20). Although trauma has been implicated in some of these cases, in other cases no evidence of trauma occurred. The fact that patients with these disorders can progress to systemic PM, remain chronically focal, or spontaneously resolve suggests that this syndrome may represent a variety of disorders with heterogeneous etiologies and pathogeneses. Similarly, myositis ossificans, in which either local or more generalized areas of soft tissue, including muscle, undergo proliferation, inflammation, and finally replacement by bone, probably represents a variety of disorders and needs additional study for definite categorization (21). A more recently identified type, macrophagic myofasciitis, is a focal form of myositis that was originally described as developing in association with aluminum hydroxide-containing vaccines but has also been reported occurring without vaccinations (22).

## Serologic Classifications

Another approach to classifying the IIMs utilizes the immune responses in these patients. The myositis autoantibodies have an important role in identifying additional groups of patients who share common features and may eventually assist in defining their pathogeneses. Table 2.2 lists a serologic classification of the IIMs using these autoantibodies and their major associations as understood today.

The more studied autoantibodies—such as the antisynthetase, anti-p155/p140, anti-MJ (autoantibody directed against nuclear matrix protein NXP-2), anti-signal recognition particle (SRP), and anti-Mi-2 autoantibodies (directed against chromodomain helicase DNA binding protein 4)—are particularly useful in that each appears to define a syndrome different enough from the others in epidemiology, clinical features, severity of myositis, immunogenetics, responses to therapy, and prognosis to be considered a distinct disorder (9,23,24). Yet additional studies of the newer myositis autoantibodies are needed to determine fully their usefulness in this regard. Overall, these myositis autoantibodies have been helpful in assisting in the diagnosis of certain patients with confusing presentations and in predicting clinical courses and responses to therapy.

Most of the studies of myositis autoantibodies have defined them by protein and RNA immunoprecipitation methods, which remain the gold standard for their

**Table 2.2** A serologic classification of the idiopathic inflammatory myopathies

Serologic category	Associations and comments
Antisynthetase <sup>b</sup>	Frequent symmetric nonerosive arthritis, interstitial lung disease, low-level fevers, mechanic's hands, Raynaud's phenomenon and often occurs as an acute, severe myositis with onset in the spring, moderate response to therapy, myositis flare with tapering of therapy; seen in 20–25% of all myositis cases
Anti-signal recognition particle	Frequent palpitations and myalgias; very acute onset of severe polymyositis; most often in black women; poor response to therapy; seen in <5% of myositis patients
Anti-Mi-2 <sup>c</sup>	Classic dermatomyositis with V sign, shawl sign, and cuticular overgrowth; good response to therapy; seen in 5–10% of myositis patients
Anti-p155/p140	Associated with dermatomyositis in children and adults and cancer in adults
Anti-MJ	Associated with dermatomyositis in children and adults
Anti-CADM-140	Japanese patients with amyopathic dermatomyositis and interstitial lung disease
Anti-PM-Scl	High incidence of scleroderma/myositis overlap syndromes
Anti-Ku70/80	Seen primarily in scleroderma/myositis overlap syndromes
Anti-U1RNP	Seen primarily in myositis overlap syndromes
Anti-U2RNP	Associated with scleroderma/myositis overlap syndromes
Anti-Ro52	Seen primarily in myositis overlap syndromes
Anti-La	Seen primarily in myositis overlap syndromes

<sup>a</sup>Modified from (53); information derived from (7,9,23,24,56–58)

<sup>b</sup>Includes patients with anti-Jo-1 autoantibodies (directed against histidyl-transfer RNA synthetase) and those with autoantibodies to threonyl-, alanyl-, isoleucyl-, glycyl-, tyrosyl-, asparaginy- and phenylalanyl-transfer RNA synthetases

<sup>c</sup>Abbreviations: *anti-Mi-2* autoantibody directed against chromodomain helicase DNA binding protein 4; *anti-p155/p140* antibody directed against transcriptional intermediary factor 1gamma; *anti-MJ* autoantibody directed against nuclear matrix protein NXP-2; *anti-CADM-140* autoantibodies directed against a 140 KD protein seen initially in clinically amyopathic dermatomyositis patients

determination but are only performed by a few laboratories. The more common tests for these autoantibodies in clinical practice, using solid-phase assays, have not been as fully validated and can result in false-positive and false-negative results ((25) and Miller, personal observations). Thus, more study is needed to assess the most cost-effective and accurate ways to identify these autoantibodies.

## Environmentally Associated Myositis

Myositis in association with environmental exposures—to drugs, toxins, or other agents—has been traditionally considered in a different category from the IIMs. Nonetheless, the lines demarcating these disorders are not clear, and environmentally associated myositis can be indistinguishable in clinical presentation, pathology, and response to immunosuppressive therapy from IIMs. Defining these forms is difficult because, although there may be a temporal association between the exposure and the development of myositis, a cause-effect relationship with the exposure and

the pathophysiologic mechanisms involved in the evolution of the inflammation are often not clear. Attempting to define an appropriate temporal association (challenge), assessing if the myositis ameliorates after removal of the suspect agent (dechallenge), determining if the myositis recurs after reexposure to the suspect agent if appropriate (rechallenge), eliminating all other possible causes for the myositis, assessing if any prior similar or identical cases have been reported, and determining if there is any biologic rationale for the association are all useful approaches to help define if there is a true association with the suspect agent (26). Given the increasing evidence that many immune-mediated disorders are the result of gene-environment interactions (27), a classification based on environmental exposure history is useful for the purpose of differential diagnosis and to increase awareness and research of these entities (Table 2.3).

**Table 2.3** An environmental classification of the inflammatory myopathies<sup>a</sup>

Environmental exposure category	Associations and comments
Penicillamine	Can mimic classic polymyositis; different genetic risk factors from primary polymyositis
Lipid-lowering agents	Most commonly associated with noninflammatory myopathies, but some polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) cases have been reported
Hydroxyurea	A dermatomyositis-like eruption is most often seen
Other drugs	Rarer reports of myositis after antithyroid agents (carbimazole, propylthiouricil); omeprazole; cimetidine; leuprolide acetate; procainamide; hydralazine; penicillin; minocycline; cytokines (interferon $\alpha$ and interleukin 2); growth hormone; and others
L-Tryptophan	A polymyositis-like syndrome was sometimes seen in the eosinophilia myalgia syndrome
Adulterated rapeseed oil	Myositis occasionally was seen in the toxic oil syndrome
Transplants (graft-versus-host myositis)	Rare reports of a polymyositis-like syndrome after bone marrow transplants and in mice
Ciguatera toxin	Three cases of polymyositis following classic ciguatera poisoning have been described
Silica	Rare cases of myositis reported in stonemasons and house cleaners
Collagen implants	Frequent dermatomyositis; onset often within 6 months of implant
Silicone implants	Frequent dermatomyositis; late onset after implants, possible different genetic predisposition from other forms of myositis
Ultraviolet radiation	Associated with DM in the first worldwide study of myositis
Physical exertion	A sixfold increase in PM/DM was seen in a case in a sibling control study
Aluminum hydroxide vaccines	Focal macrophagic myofasciitis and diffuse inflammatory myopathy with abundant macrophages are described occurring after receiving vaccines containing aluminum hydroxide

<sup>a</sup>Modified from (53); information derived from (27,31–33,59–63); categories are not mutually exclusive



While a wide array of infectious agents, including bacteria, viruses, and parasites, has also been associated with myositis, these agents are considered infectious myopathies responsive to anti-infective therapy and are not covered in this review.

Drug-associated myositis has been increasingly identified as the number of agents in use multiplies and associations have become better known. The prototypic example of penicillamine-induced myositis is well documented as an entity that usually responds to dechallenge but can cause fatal complete heart block (28). Although the dose of the drug does not appear to be a factor in development of myositis, the immunogenetic risk factors for the development of myositis after penicillamine exposure appear to differ from those of idiopathic myositis (29).

Most classes of lipid-lowering agents have been associated with myopathies, but smaller numbers of cases of PM, DM, and IBM have also developed in subjects taking these agents (30). The role of other drugs in inducing myositis, such as antithyroid agents (carbimazole, propylthiouricil); omeprazole; cimetidine; leuprolide acetate; procainamide; hydralazine; penicillin; minocycline; cytokines (interferon- $\alpha$  and interleukin [IL] 2); and growth hormone are only based on case reports and remains less clear (31–33).

Other relatively rare environmentally associated IIMs listed in Table 2.3, which may be distinct entities but need additional study to clarify their nature, include myositis occurring after transplantation (graft-versus-host myositis); the myositis associated with the L-tryptophan-related eosinophilia myalgia syndrome and the toxic oil syndrome; other toxin-associated myositis; myositis developing after silica exposure in stonemasons and house cleaners; and the myositis, especially DM, that occurs after collagen and silicone implants. Of interest, the myositis that develops after silicone implants appears to be associated with a different genetic risk factor, human leukocyte antigen (HLA) DQA1\*0102, compared to the genetic risk factors seen in other forms of IIMs (34).

## Genetic Classifications

A genetic role for the development of myositis has been suspected for some time based on early immunogenetic associations and familial forms (35,36). Yet, although these immunogenetic associations have been known for several decades, the specific major histocompatibility complex (MHC) loci associated with the many different IIM phenotypes have only recently been elucidated. While the ancestral MHC 8.1 haplotype defined by HLA A\*0101-B\*0801-Cw\*0701-DRB1\*0301-DQA1\*0501 has been confirmed to be a risk factor for all forms of myositis in Caucasians, the major clinical and serologic subgroups in different ethnic groups have different immunogenetic associations (37–46). There is also increasing evidence that polymorphic genes beyond those regulating the immune system in the MHC are likely important in the development of one or more forms of myositis. These other genes, which play important regulatory roles in immune activation and regulation, include those for tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), IL-1 $\alpha$ , IL-1 $\beta$ , IL-1RN, interferon

gamma (IFN $\gamma$ ), protein tyrosine phosphatase N22, and immunoglobulin (Ig) G and IgK constant gene polymorphisms (35,47–50); however, this review focuses on how MHC and immunoglobulin gene associations can help classify the IIMs given their more extensive evaluation in the clinical and serologic groups. Studies of a number of autoimmune diseases suggested that gene-environment interactions are likely critical for the development of subgroups of disease (27); therefore, a focus on only the environment or genetics alone may be limiting. Nonetheless, given our inability to detail these interactions now, it is useful to consider how genetics alone can help in dividing and understanding the myositis syndromes.

The best-studied genetic markers for myositis are HLA alleles, and a division of IIM phenotypes based on currently identified major HLA genetic factors is summarized in Table 2.4. It is clear that the risk factors differ in many of the different clinical and serologic groups, and in some cases more than one HLA allele is involved in increasing risk for the development of myositis. In addition, a growing number of protective factors, which are alleles seen in higher frequency in controls compared to myositis subjects, have been identified in myositis patients as a whole as well as in the various phenotypes. Thus, it very well may be that a combination of multiple genetic risk factors, along with the absence of protective factors, is important to allow for the expression of disease (51).

Polymorphic determinants of genes encoding constant regions of immunoglobulin gamma heavy and kappa light chains (GM and KM loci on human chromosomes 14q32.33 and 2p12, respectively) have been associated with different immune responses in a variety of infectious and autoimmune diseases in various ethno-geographic populations (52). GM and KM associations have been described in both Mesoamerican and Korean IIM populations (37,38). Recently, additional associations have been seen in Caucasian and African American myositis populations and have been found to differ in some of the clinical and serologic subgroups (Table 2.4) (50). While the physiologic mechanisms underlying these associations remain uncertain, several studies have identified higher serum titers of specific subclasses of IgG antibodies (i.e., IgG1, IgG2, IgG3) directed against antigenic epitopes of infectious disease agents or self-proteins in persons with specific GM and KM markers.

These candidate gene approaches have identified a number of alleles that increase or decrease risk for development of myositis and the associated subgroups. Due to the polygenic and complex nature of these risk factors and the additional roles of environmental and other factors, none of the current genetic risk factors can be used as a tool for accurately predicting development of disease. Yet, these factors are currently being studied in an attempt to decipher pathogenetic mechanisms. International collaborations are already under way utilizing genomewide association studies in large populations of well-defined patients to expand understanding of the genes linked to myositis and possibly develop novel diagnostic, pathogenic, and therapeutic approaches to the IIMs in the future.

**Table 2.4** A genetic classification of the idiopathic inflammatory myopathies<sup>a</sup>

	All IIMs	PM	DM	IBM	JDM	Anti-Jo-1	Anti-PL7	Anti-Mi-2	Anti-p155	Anti-SRP
HLA loci										
Ancestral	8.1	8.1	8.1	8.1	8.1	8.1	NA	NA	NA	NA
haplotype										
Other class I	B*0702	B*44	A*68	B*35						
		C*0701	B*15	C*14						
Other class II	DQA1*0301	DQA1*0201	DQA1*0301	DRB1*0701	NA	C*04	C*0304	NA	NA	B*5001
		DQA1*0401	DQA1*01	DRB1*03	DQA1*0301	DRB1*0701	DRB1*1501	DRB1*0701	DQA1*0301	DQA1*0104
				DQA1*0201	DQA1*0201	DQA1*0201	DQA1*0501			
Immunoglobulin genes										
GM/KM	3 23 5,13/1	3 23 5,13/1	3 23 5,13	NA	3 23	3 23 5,13	3	NA	NA	NA
markers					5,13/1,1					

<sup>a</sup>Information derived from (39–41,43,45,46,50,58); only data for Caucasians and the primary significant associations based on corrections for multiple comparisons or random forest evaluations are shown; alleles in italics are protective for the development of the phenotype. *PM* polymyositis; *DM* dermatomyositis; *IBM* inclusion body myositis; *JDM* juvenile DM; *anti-Jo-1* autoantibodies to histidyl-tRNA synthetase; *anti-PL7* autoantibodies to threonyl-tRNA synthetase; *anti-Mi-2* autoantibodies directed against chromodomain helicase DNA binding protein 4; *anti-p155* autoantibodies are directed against transcriptional intermediary factor 1gamma; *anti-SRP* autoantibodies to the signal recognition particle; the 8.1 ancestral haplotype consists of HLA A\*0101-B\*0801-Cw\*0701-DRB1\*0301-DQA1\*0501; NA not applicable (no significant associations seen)

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