

# Update on the genetics of the idiopathic inflammatory myopathies

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A number of lines of investigation suggest that, as is likely the case for other autoimmune diseases, the idiopathic inflammatory myopathies (IIM) develop as a result of specific environmental exposures in genetically susceptible individuals.

Current data imply that multiple genes are involved in the etiology of these complex disorders. Targeted gene studies and whole genome approaches have begun to identify several genetic risk factors for autoimmune diseases, but the rarity and heterogeneity of the IIM have limited our knowledge of their associated genes. Current findings suggest that human leukocyte antigen (HLA) genes on chromosome 6, particularly HLA DRB1\*0301 and the linked allele DQA1\*0501, have the strongest associations with all clinical forms of IIM in white patients. Different HLA alleles, however, may confer risk or protection for myositis in distinct ethnic, serologic, and environmental exposure groups. Non-HLA genetic risk factors, which have been documented for other autoimmune diseases, are now being identified for the IIM. These include polymorphic genes encoding immunoglobulin heavy chains (defined by serologic markers known as Gm allotypes), cytokines and their receptors, and certain proteins that accumulate in the myocyte vacuoles of inclusion body myositis patients. Selected allelic polymorphisms of interleukin-1 receptor antagonist variable number tandem repeats and genes for tumor necrosis factor alpha and interleukin-1 alpha also have recently been associated with IIM. The pathogenic bases for the differences among the many clinically, pathologically and immunologically defined syndromes known as the IIM will be elucidated through a better understanding of the multiple genes that define risks for their development, as well as through investigations of gene-gene and gene-environment interactions. *Curr Opin Rheumatol* 2000, 12:482-491 © 2000 Lippincott Williams & Wilkins, Inc.

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*Current Opinion in Rheumatology* 2000, 12:482-491

## Abbreviations

apoE	apolipoprotein E
DM	dermatomyositis
HLA	human leukocyte antigen
IBM	inclusion body myositis
IIM	idiopathic inflammatory myopathies

IL-1RN	interleukin-1 receptor antagonist
JRA	juvenile rheumatoid arthritis
MHC	major histocompatibility complex
MSAs	myositis-specific autoantibodies
PM	polymyositis
TNF- $\alpha$	tumor necrosis factor alpha

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The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare systemic connective tissue diseases that are defined by the presence of acquired muscle weakness and chronic inflammation of unknown cause. Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) are the most common clinical forms of these diseases and they are likely increasing in prevalence [1]. The frequency of the clinical and serologic subsets, as well as the risk factors for developing IIM, may differ among distinct ethnic groups in geographically isolated parts of the world [2,3,4,5].

The pathogenesis of the IIM remain unclear, although evidence from family, cohort, and candidate gene studies suggest a genetic component and that many different genes are likely necessary for the development of these diseases [6]. Current findings imply, however, that genetic factors themselves are not adequate for the development of disease. Rather, in genetically predisposed individuals, disease probably develops only after exposure to critical environmental triggers [7,8]. In this article, we summarize the current understanding of the genetics of the IIM. The genetics of the familial noninflammatory forms of the inclusion body myopathies, which are not considered IIM, will not be covered here, but have been recently reviewed elsewhere [9].

## Approaches to the study of genetic risk factors for autoimmune disease

Several approaches have been used to assess the role of genetics in the development of autoimmune diseases and some of these have been applied to the IIM (Table 1) [6]. The oldest is the simple description of the same autoimmune disease occurring in multiple members of a single family. These multicase families with autoimmunity suggest a genetic etiology and/or shared environmental factors in the pathogenesis of these diseases. In recent decades, familial associations of several autoimmune diseases, including IIM, have been reported. To date, a total of 34 families in which two or more members have

**Table 1. Approaches to assess the genetics of autoimmune diseases**

Approach	Examples in IIM	Examples in other autoimmune diseases
Reports of multicase families with the same autoimmune disease	34 families reported with $\geq$ two cases of PM, DM, IBM, amyopathic DM, or orbital myositis [6•,24,25]	IDDM: Mennonite kindred [64] RA: Four generations of women in one family with RA [65]
Studies of concordance rates in monozygotic twins vs dizygotic twins	No studies to date	IDDM: 53% concordance in MZ twins vs 11% in DZ twins [66] RA: 15% concordance in MZ twins vs 4% in DZ twins [67]
Genetic investigations of multicase families with the same autoimmune diseases	HLA DRB1*0301 and homozygosity of HLA DQA1 are risk factors for familial IIM [29]	MS: DR2 is a risk factor for familial and sporadic MS [68]
Candidate gene studies	MHC genes primarily investigated; HLA DRB1*0301 and DQA1*0501 are major risk factors (see Tables 3,4) Non-MHC genes beginning to be identified (see Table 5)	IDDM: HLA DQB1*0302-DR1*0401/DQB1*0201-DRB1*03 genotype is thought to be the major genetic risk factor in Europe [69] SLE: Non-MHC genes, including IL-10, have been identified [70]
Whole genome scans	No studies to date	Preliminary genome scans performed for SLE, RA, JRA, and AS [71]

AS, ankylosing spondylitis; DM, dermatomyositis; DZ, dizygotic; HLA, human leukocyte antigen; IBM, inclusion body myositis; IDDM, insulin-dependent diabetes mellitus (type 1); IIM, idiopathic inflammatory myopathy; IL, interleukin; JRA, juvenile RA; MHC, major histocompatibility complex; MS, multiple sclerosis; MZ, monozygotic twins; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

an IIM, including DM, PM, IBM, orbital myositis, or amyopathic myositis, have been published (Table 1).

Other approaches used to investigate the genetics of complex disorders include studies of disease concordance in monozygotic and dizygotic twins. Although the rarity of the IIM has prohibited such studies from being performed, twin studies in other autoimmune diseases have shown concordance rates to be higher in monozygotic than in dizygotic twins, but still less than 50% in most cases [6•]. These findings suggest important roles for both genetic and environmental factors in the pathogenesis of many autoimmune diseases. Genetic investigations of familial autoimmune diseases, in which multiple cases of a particular autoimmune disease are present within a single family, have led to interesting findings. These include: (1) in many diseases, the same genetic risk factors are often present in familial as in sporadic cases [10], although in some disorders, unique risk factors have been identified for the familial forms [11]; (2) the same genotypes can predispose to many different autoimmune disease phenotypes as well as to other diseases that are not thought to be autoimmune [12]; and (3) in some cases, serologic and genetic screening techniques can accurately predict the likelihood of familial disease [13].

In addition to the observation that the same autoimmune disease can be found within a given family, a tendency for multiple different autoimmune diseases to occur with increased frequency among first and second degree relatives of a proband with a given autoimmune disease has also been described [14,15]. These reports imply that there are common genes predisposing to many forms of autoimmunity, as has been demonstrated by meta-analyses of whole genome scanning studies

[16]. In addition to these shared autoimmunity predisposing genes, however, other genes and/or environmental exposures likely determine which specific autoimmune disease an individual will develop [6•,16].

Candidate gene studies, using cohort comparisons between affected patients and racially- and geographically-matched healthy controls to assess potential disease-associated genes based upon suspected pathogenic mechanisms, have shown that the major histocompatibility complex (MHC) region on chromosome 6 has the strongest association with most immune-mediated diseases. In some cases, these risk factors have also been confirmed by family-based methodologies, such as transmission disequilibrium testing, in which unaffected parents are used as controls [17]. Through candidate gene approaches in cohort-based studies, other polymorphic genetic loci, including genes encoding cytokines and their receptors, T-cell receptors, immunoglobulins, Fc receptors, and autoantigens have been identified as risk factors for various autoimmune diseases, but their statistical associations with disease are weaker than those of the MHC [18,19]. The data overall, however, suggest that many of these other genetic loci are involved as secondary risk factors [16,20••,21•]. Candidate gene approaches, which constitute the primary data that have been used to identify immunogenetic risk factors for the IIM, are detailed below.

The most recent genetic approaches have involved whole genome scans in multiple-case families with single autoimmune diseases (Table 1), or in animal models of inherited autoimmune diseases. These studies have assessed microsatellite or other markers on all chromosomes for linkage to particular phenotypes (reviewed in [6•]), and suggest that perhaps several

dozen genes may play a role in the development of many autoimmune disorders [16]. The rarity of multicase families with IIM and the lack of an appropriate animal model have not allowed such genome-wide scans to be performed in IIM.

### Evidence for familial idiopathic inflammatory myopathy and familial autoimmunity in pedigrees of idiopathic inflammatory myopathy probands

Although the initial clinical descriptions of myositis occurred in the 1800s [22], the first report of myositis affecting multiple family members was not published until 1953, when Wedgewood noted juvenile DM in twins with disease onset within 1 year [23]. Over the next several decades, similar aggregations in first-degree family members of other clinical forms of myositis, including PM, DM, IBM, orbital myositis, and amyopathic DM [6•,24,25], as well as IIM among more distant relatives [6•] were described (Table 2). In 1991, a report of concurrent onset of PM in four family members living in the same rural location emphasized both the likely genetic and environmental aspects of this disease [26]. In the subsequent year, a kindred study implied a possible autosomal dominant inheritance pattern for some types of IBM [27]. To date, a total of 34 families in which two or more members have IIM have been reported [6•,24,25].

A study of all forms of familial IIM compared a large number of multicase IIM families (36 IIM patients with PM, DM, or IBM from 16 unrelated families in which two or more family members have an IIM) to sporadic IIM (181 unrelated cases) with regard to clinical features, serology, and immunogenetic risk factors [11]. Of interest, in most of the familial IIM patients, the same clinical group was shared among all members of a given family who developed myositis. The sporadic IIM group had a higher frequency of myositis-specific autoantibodies (MSAs) compared with familial IIM, and after adjustment for the clinical associations with the MSAs, no significant clinical differences were observed between the familial and sporadic IIM groups. HLA DRB1\*0301 was a risk factor for familial IIM, as is the case for sporadic IIM; however, homozygosity of DQA1 was an additional unique risk factor for familial forms of myositis [28].

In 1997, Pachman *et al.* [29] assessed histories for autoimmune diseases in family members of juvenile rheumatoid arthritis (JRA), juvenile DM patients with sporadic disease, and geographically matched healthy controls. They noted that pedigrees of children with JRA had a significantly higher frequency of rheumatoid arthritis and pernicious anemia than controls, but this was not observed in the juvenile DM families.

**Table 2. Highlights of the chronology of published reports of multicase idiopathic inflammatory myopathy failure**

Study	Comments
Wedgewood <i>et al.</i> [23], 1953	First report of familial IIM; juvenile DM in twins
Winkler [72], 1956	First report of nontwin familial IIM; siblings with juvenile DM
Lambie and Duff [73], 1963	First report of juvenile DM in cousins
Hennekam <i>et al.</i> [74]	First report of juvenile DM cousins living in different towns
Harati <i>et al.</i> [75], 1991	First report of four family members in same household developing PM, with possible association with local rodents
Massa <i>et al.</i> [76], 1991	First report of IBM in siblings
Neville <i>et al.</i> [27], 1992	First report of a large kindred with IBM, suggesting an autosomal dominant inheritance pattern
Rider <i>et al.</i> [11], 1998	Largest study of familial IIM (16 multicase families); new findings included: a lower frequency of MSAs, but no difference in clinical features; DRB1*0301 is a shared risk factor with sporadic IIM, but homozygosity of the DQA1 allele is a unique risk factor for familial IIM
Ginn <i>et al.</i> [14], 1998	First report of increased frequency of other autoimmune diseases in pedigrees of IIM patients
Plamondon <i>et al.</i> [25], 1999	First report of juvenile DM and amyopathic DM in siblings who share DQA1*0501
Maurer and Zierz [24], 1999	Report of four family members with orbital myositis

DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; MSAs, myositis-specific autoantibodies; PM, polymyositis.

The first study to assess the frequency of all autoimmune diseases in families of sporadic IIM patients was published in 1998 [14]. This prospective case-controlled investigation demonstrated that the prevalence of autoimmune disease was significantly higher (21.9%) in the 151 first-degree relatives of 21 IIM patients compared with that in 143 first degree relatives of 21 age-, gender- and race-matched probands without evidence of an autoimmune disease (4.9%) [14]. As expected, these pedigrees also demonstrated a female predominance for autoimmunity, an increase in frequency of autoimmune diseases with increasing age, and, through genetic modeling, that autoimmune diseases in these families likely have a polygenic mode of inheritance.

### Evidence that HLA alleles are risk factors for idiopathic inflammatory myopathy

Although hereditary aspects of myositis were recognized half a century ago, only in the last two decades have laboratory approaches been applied in an attempt to identify the specific genes responsible for the development of the IIM (Tables 3,4). Of the many polymorphic genetic loci that may be risk factors for myositis and other autoimmune diseases, the HLA region on chromo-

some 6 appears to encompass the strongest risk factor. As with other complex disorders [21•], many non-HLA polymorphic loci are also likely to be involved in the pathogenesis of the IIM (Table 5).

HLA B8, an MHC class I allele defined by serologic methods, was the first genetic marker associated with IIM in a study of patients with juvenile DM [30]. As serologic HLA testing evolved into molecular techniques and larger numbers of patients were studied, this initial finding was discovered to be more likely due to linkage disequilibrium with HLA class II genes, because HLA A1;B8;Cw7;DRB1\*0301;DQA1\*0501;C4A\*Q0 constitutes a common extended haplotype in white populations [30,31]. HLA DRB1\*0301 and DQA1\*0501 have now been determined to be risk factors for all the major clinical forms of sporadic and familial IIM in both white adults and children in the US and Europe [2,30–33]. Some of these results from cohort-control studies have

also been confirmed by transmission disequilibrium testing analysis of sporadic juvenile DM families [31]. Recently, in a small, single-center study, other HLA Class II alleles, DMA\*0103 and DMB\*0102, have been identified as possible risk factors for juvenile DM in white patients [34••].

Small studies of ethnic minorities in the US have shown HLA DQA1\*0501, but not DRB1\*0301, to be a risk factor for adult IIM and juvenile DM in black patients [32,35]. HLA DQA1\*0501 has also been found to be increased in Hispanic juvenile DM patients compared with controls [35], but not in Hispanic adult IIM subjects [32]. In other ethnic groups living outside the US, different genes appear to be risk factors for the IIM. In Korean IIM patients, for example, despite their clinical and serologic similarity to US white IIM subjects, no HLA allele has been identified as a risk factor. HLA DRB1\*14, however, is a unique protective factor for

**Table 3. Human leukocyte antigen association with idiopathic inflammatory myopathy clinical groups**

Clinical group (race)	Associated alleles <sup>†</sup>	Comments <sup>‡</sup> [references]
IIM, PM, DM (white)	DRB1*0301, DQA1*0501, DQB1*0201 <sup>9</sup> EYSTS <sup>13</sup> , DRB1 HVR motif DR3, DRw52 C4A*Q0 DR3 (possible B8) DRB1*0201 and *0501 (protective factor) DR4 (protective factor) <sup>¶</sup>	OR = 2.3 – 11.2 (2.4 – 19.7); P = 0.02 – 10 <sup>-17</sup> [2,3•,11,32] OR = 3.1 (1.8-5.4); Pc = 4.7 × 10 <sup>-4</sup> [3•] P < 0.001 [33] <sup>§</sup> RR = 2.7, P = 0.08 [77] P = 0.003, PC = 0.02 (for B8: P = 0.005, Pc = NS) [78] P < 0.001 [2] <sup>§</sup> Pc = 0.04 [78]
Familial IIM (mixed) IBM (white)	DQA1 homzygosity Locus between DR and C4 DRB1*0301, DRB3*0101, DQB1*0201 B8, C4A*Q0, DR3, DRw52 DR3 (possible DR1, DR6, DQ1)	OR = 4.2 (1.7-10.2), Pc = 0.002 [11] Statistics not available [20] P < 0.01 [79] P < 0.01 [50] Statistics not available [33]
Juvenile DM (white)	DMA*0103; DMB*0102 DQA1*0501 DQA1*0501, DR3 C4A*Q0 B8	RR = 5.7, Pc = 0.0016, RR = 8, P = 0.036, Pc = 0.19 [34] TDT analysis, P < 9 × 10 <sup>-4</sup> [35,80] P = 0.024 [31,81] P < 0.001 [82] RR = 2.8; Pc < 0.01 [30]
IIM, PM (black)	DQA1*0501, and/or DQA1*0401 C4A*Q0 B7; DRw6	OR = 2.7, P = 0.01, Pc = 0.09 [32] RR = 1.8, P = NS [77] P = 0.02, Pc = NS, P = 0.005, Pc = 0.04 [78] P < 9 × 10 <sup>-4</sup> [35]
Juvenile DM (black)	DQA1*0501	P < 9 × 10 <sup>-4</sup> [35]
IIM, PM, DM (Hispanic)	No HLA association detected.	[32]
Juvenile DM (Hispanic)	DQA1*0591	P < 9 × 10 <sup>-4</sup> [35]
IIM (Meso-American)	DQA1*01 (protective factor)	P < 0.001, Pc = 0.006 [4]
Juvenile DM (Latin American)	DR3	P < 0.05 [81]
IIM (Korean)	No HLA association detected.	[3]
IIM (Japanese)	B7 DQA1*0501 (protective factor) DQB1*0301 (protective factor)	OR = 3.4 (1.1 – 10.7); P = 0.02, Pc = NS [5] OR = 0.32 (0.099 – 1.0), P = 0.04, Pc = NS [5] OR = 0.36 (0.15–0.89), P = 0.02, Pc = NS [5]
PM (Japanese)	CW3 (compared with DM) A24 (protective factor)	OR = 3.0 (1.1 – 8.8), P = 0.03, Pc = NS [5] OR = 0.3 (0.11 – 0.87); P = 0.02, Pc = NS [5]
DM (Japanese)	DRB1*08 DR 59	OR = 2.3, P = 0.004 [5] OR = 14.3; P = 0.01, Pc = NS [5]
Overlap (Japanese)	B7 DRB1*0101	OR = 8.1 (1.93–34.0), P = 0.005, Pc = NS [5] OR = 3.5 (1.03–3.67); P = 0.04, Pc = NS [5]

<sup>†</sup>Although the data currently suggest stronger associations with the HLA Class II alleles than with the HLA class I alleles, there has not been a formal comparison of the strength of association of these linked alleles on the common white haplotype HLA.

A1;B8;Cw7;DRB1\*0301;DQA1\*0501;DQB1\*0201;C4A\*Q0. <sup>§</sup>95% confidence interval is enclosed in parentheses when available. <sup>§</sup>P value calculated from published data. <sup>¶</sup>Data for all races combined.

DM, dermatomyositis; IBM, inclusion body myositis; HLA, human leukocyte antigen; HVR, hypervariable region; IIM, idiopathic inflammatory myopathy; NS, not significant; OR, odds ratio; Pc, P value corrected for multiple comparisons; RR, relative risk; TDT, transmission disequilibrium test.

**Table 4. Human leukocyte antigen associations with idiopathic inflammatory myopathy serologic groups**

Serologic group (race)	Associated alleles	Comments [reference]
MSA positive (white) <sup>†</sup>	<sup>9</sup> EYSTS <sup>13</sup> DRB1 HVR1 motif	OR = 4.4, <i>P</i> = 0.02 [32]
Anti-Jo-1 (white)	DRB1*0301; DQB1*0201 <sup>‡</sup> DR3 and/or DRw6 DR3, DQ2	OR = 9.6, <i>P</i> = 3 × 10 <sup>-5</sup> ; OR = 8.3, <i>P</i> = 4 × 10 <sup>-4</sup> [32] <i>P</i> ≤ 0.01 [83] <i>P</i> ≤ 0.001 [33]
Anti-Jo-1 (black, Hispanic, and white)	DQA1*0501 and/or DQA1*0401	OR = 7.4, <i>P</i> = 1 × 10 <sup>-5</sup> [32]
Anti-Mi-2 (white)	DQA1*0501 DRB1*07 <sup>§</sup> DRB1*07 homozygosity DQA*0201 <sup>§</sup> DRB1 9 <sup>HP</sup> homozygosity DR7, DRw53	OR = 5.8, <i>P</i> = 1 × 10 <sup>-5</sup> [32] OR = 22 (4.6–105), <i>P</i> < 1 × 10 <sup>-4</sup> [36] OR = 84 (4.3–1616), <i>P</i> < 1 × 10 <sup>-4</sup> [36] OR = 20 (4.4–93), <i>P</i> < 1 × 10 <sup>-4</sup> [36] OR = 25 (6.2–99), <i>P</i> < 1 × 10 <sup>-4</sup> [36] <i>P</i> <sub>c</sub> < 0.001 [33]
Anti-SRP (mixed)	DR5, DQA1*0301, DRw52	<i>P</i> ≤ 0.05 compared to antisynthetases [33]
Anti-PM/Scl (white)	DRB1*0301 DQA1*0501 DR3 DR3	<i>P</i> <sub>c</sub> = 0.012 and 0.008, respectively [2] <i>P</i> < 0.0001 [84] RR = 10.6, <i>P</i> < 0.001 [85]
Anti-Ku (white)	DRB1*0301, DQA1*0501 DQw1	<i>P</i> <sub>c</sub> < 0.008 [2] RR = 5.8, <i>P</i> = 0.01 [86]
MSA negative (Korean)	DRB1*14 (protective factor)	OR = 0.046 (0.003–0.77) [3•]

<sup>†</sup>MSA+ includes anti-Jo-1, PL-12, OJ, EJ, KJ, transfer RNA, and SRP. <sup>‡</sup>Although the data currently suggests stronger associations with the HLA Class II alleles than with the HLA class I alleles, there has not been a formal comparison of the strength of association of these linked alleles on the common white haplotype HLA A1:B8;Cw7;DRB1\*0301;DQA1\*0501;DQB1\*0201;C4A\*Q0. <sup>§</sup>DR7 and DQA1\*0201 are linked alleles. HVR, hypervariable region; MSA, myositis-specific autoantibodies; OR, odds ratio; *P*<sub>c</sub>, *P* value corrected for multiple comparisons; PM, polymyositis; RR, relative risk; TDT, transmission disequilibrium test.

myositis in Korean patients without MSAs [3•]. In Japanese patients, HLA B7 has been reported to be a genetic risk factor for the development of IIM, and DQA1\*0501 is, surprisingly, a protective factor [5], whereas in Meso-American patients HLA DQA1\*01 may be a protective factor [4].

Myositis-specific autoantibodies appear to define syndromes with associated clinical features, prognoses, and responses to treatment [33] (see the review by Targoff in this issue [pp 475–481]). As is the case in other autoimmune disorders, different HLA class II alleles serve as risk factors for the development of differ-

ent autoantibodies (Table 4). For example, antisynthetase autoantibodies are associated with DRB1\*0301 (OR = 9.6) and DQA1\*0501 (OR = 5.8) in white patients [32]. In black and Mexican American patients, HLA DQA1\*0501 and/or DQA1\*0401 are increased in frequency in patients with anti-Jo1 autoantibodies compared with controls, but DRB1\*0301 was not identified as a risk factor (although this study is limited in power) [32]. In contrast, patients with other autoantibodies have other immunogenetic risk factors. Anti-Mi-2 autoantibodies are associated with HLA DR7 (OR = 84) and the linked allele HLA DQA1\*0201 (OR = 20) in white patients [36], whereas patients with anti-signal

**Table 5. Non-HLA polymorphic genetic marker associations with the idiopathic inflammatory myopathies**

IIM group (race)	Gene/chromosome/allele	Comments [reference]
Juvenile IIM (white)	IL1RN/2/IL1RN A1	OR = 2.5, 95% CI = 1.1 - 5.8; <i>P</i> <sub>c</sub> = 0.037 [44]
Juvenile IIM (black)	IL1RN/2/IL1RN A3	OR = 6.5, 95% CI = 1.1 - 40.3 <i>P</i> <sub>c</sub> = 0.07 [44]
Juvenile DM (white)	TNF-α-308/6/TNF2 (-308A)	A risk factor for juvenile DM in white patients, increased in frequency in patients with a chronic disease course ( <i>P</i> = 0.001), calcinosis ( <i>P</i> = 0.017) [49,57]
IIM (Korean)	GM/14/Gm21 allotype	OR = 0.3, 95% CI = 0.13–0.7 [3•] No GM phenotype or allotype is a risk or protective factor in white patients
Juvenile IIM (white)	TNFα-238/6/TNF2 (-238A)	OR = 5.2, <i>P</i> <sub>c</sub> ≤ 0.0002; in linkage disequilibrium with DRB1*0301 [45]
IBM (white)	PRNP/20/M/M <sup>†</sup>	OR = 0.023 [50,87]
Juvenile IIM (white)	TNF-α-238/6/TNF2	OR = 5.2, <i>P</i> <sub>c</sub> < 0.002; in linkage disequilibrium with DRB1*0301 [45]
Juvenile IIM (white)	I IL-1-α/2/IL-1-α 1	RR = 0.25, <i>P</i> <sub>c</sub> < 0.003 (a protective factor) [45]
Juvenile IIM (white)	I IL-1-α/2/IL-1-α 1,2	RR = 4, <i>P</i> <sub>c</sub> = 0.003 (heterozygosity is a risk factor) [45]
Juvenile IIM, Anti-Jo-1 positive (white)	IL-1β-511/2/IL-1β 1,2	Heterozygosity seen in 5/5 patients, but is not significant
IBM (white)	APOE/19/ε4	<i>P</i> < 0.05 [55]

All studies unconfirmed to date. <sup>†</sup>Methionine homozygosity.

APOE, apolipoprotein E allele; DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; IL-1-α, interleukin-1 alpha; IL1RN, gene encoding interleukin-1 receptor antagonist; OR, odds ratio; *P*<sub>c</sub>, *P* value corrected for multiple comparisons; OR, odds ratio; PRNP, prion protein gene allele; RR, relative risk; TNF-α, tumor necrosis factor alpha; VNTR, variable number tandem repeat.

recognition particle autoantibodies have an increased frequency of HLA DR5 and DQA1\*0301 compared with normal controls [33]. White IIM subjects with anti-PM-Scl and anti-Ku autoantibodies have higher frequencies of HLA DRB1\*0301 and DQA1\*0501 alleles compared with controls (Table 4). Genetic studies of other IIM serologic groups have not yet been reported.

Though gene-environment interactions are inherently difficult to study in rare diseases, certain HLA class II alleles may be risk factors for IIM associated with particular environmental exposures. Furthermore, the genetic risk factors for the development of myositis after certain exposures may differ among distinct racial groups, as may be the case with D-penicillamine [37]. In white patients from the US and in patients from the Indian subcontinent, DR2 appears to be associated with development of myositis after D-penicillamine exposure [37,38]. In the later group, DQw1 also appears to be a risk factor. In white subjects in Australia, however, HLA DR4, B18, and B35 were associated with the development of myositis after D-penicillamine exposure. A small retrospective comparison study noted that white women who developed myositis after silicone breast implantation had a higher frequency of HLA DQA1\*0102, compared with race-matched controls or white IIM patients without implants [28]. These studies, though limited in power by their size, suggest the importance of both genetic and environmental components in the pathogenesis of myositis in some individuals.

### Evidence that non-HLA alleles are risk factors for idiopathic inflammatory myositis

Non-HLA loci, which have been defined as likely risk factors for other autoimmune diseases [16,18,39], may also play a role in the pathogenesis of the IIM [3•,39–41] (Table 5). Risk factors for other autoimmune diseases include genes encoding cytokines and their receptors, immunoglobulins, and loci containing a large number of genes whose functions remain unclear [3•,39]. To date, few such loci have been studied in the IIM, and the published associations are preliminary and require confirmation. The likelihood that the non-HLA genes will have much weaker associations with disease than the HLA genes suggests that very large populations of patients and race-matched controls will be needed to identify most of the polygenic risk factors for IIM.

Gm allotypes are serologic markers on IgG heavy chains encoded on chromosome 14 and thought to be associated with the regulation of immunoglobulin responses to certain exposures. They have been defined as markers for a number of autoimmune, infectious and malignant diseases [41]. Gm 21 has recently been shown

to be a protective factor for IIM in Koreans, but not in white patients in the US [3•].

The gene encoding the interleukin-1 receptor antagonist (IL-1RN), located on chromosome 2, has five allelic polymorphisms (A1–A5) of an 86 base pair variable number tandem repeat in intron 2 which represent two to six copies of the repeat sequence [42,43]. The specific allele IL-1RN A1, which is defined by four copies of the variable number tandem repeat, has been shown to be a risk factor for juvenile IIM in white patients (OR = 2.5) [44••]. This allele is not increased in black patients, but IL-1RN A3, representing five repeats, is a possible risk factor in this ethnic group [44••]. In contrast to studies of other autoimmune diseases, the IL-1RN A2 has not been identified as a severity factor for juvenile IIM [44••]. A second polymorphic gene on chromosome 2, IL-1 $\alpha$  1,2 (defined by a single G to T substitution in exon 5), has also been identified as a possible risk factor in juvenile IIM in white patients [45]. In contrast, no alleles of the polymorphic IL-1 $\beta$  gene have been identified as risk or protective factors in white juvenile IIM patients.

Tumor necrosis factor alpha (TNF- $\alpha$ ), encoded within the MHC, plays a number of important roles in the regulation of normal and pathologic immune responses. The promoter region of TNF- $\alpha$  has two polymorphic sites at nucleotide positions -238 and -308 (referred to as TNF1 and TNF2 at each site). At both nucleotide positions, TNF2 is distinguished from TNF1 by a G to A substitution. Thus, the two alleles at position -238 are named TNF1 (-238G) and TNF2 (-238A), and the two alleles at -308 are referred to as TNF1 (-308G) and TNF2 (-308A). The TNF2 (-238A) allele appears to be a possible risk factor for juvenile IIM in white patients, although this finding may be due to its linkage with DRB1\*0301 [45]. The other polymorphism of the TNF- $\alpha$  gene, resulting from a G to A substitution at position -308, appears to be a risk factor for juvenile DM in white patients [45]. Homozygosity of TNF (-308A) confers a high risk of death or severe neurologic involvement in patients with cerebral malaria [46]. This allele may also be a risk factor for systemic lupus erythematosus and several other autoimmune diseases [43,47]. Furthermore, in patients with juvenile DM, TNF2 (-308A), which is associated with higher levels of TNF- $\alpha$  after *in vitro* stimulation of peripheral lymphocytes, is increased in white patients with calcinosis, a chronic disease course, and capillary occlusion on biopsy, suggesting the -308 TNF- $\alpha$  allele may be a severity factor [45,48,49•].

HLA DRB1\*0301 appears to be an important risk factor for sporadic inflammatory forms of IBM, but not for the hereditary noninflammatory forms of the inclusion body myopathies [50]. Nonetheless, recent findings imply that

non-HLA genes may also play a role in the pathogenesis of IBM, the most common form of IIM in the elderly. IBM is characterized on muscle biopsy by intracellular inclusions containing many components. The prion protein has been found to be one constituent of these intracellular inclusions and is encoded by a polymorphic gene, which results in a protein containing either a methionine or valine at codon 129 [51]. An unconfirmed study has recently suggested that homozygosity at codon 129 (encoding methionine) of the prion gene may be a predisposing factor for IBM [52••]. This is of interest because overexpression of the prion gene in transgenic mice leads to a pathologic state similar to IBM [53]. An additional protein component of the intracellular rimmed vacuoles of IBM is apolipoprotein E (apoE), which is also found in the brain plaques of patients with Alzheimer disease [54]. The major known function of apoE is the transport of lipoproteins in the blood. In humans, 3 major isoforms are found: E2, E3 and E4. The single amino acid differences between the apolipoprotein isoforms confer differing affinities for apoE receptors as well as for lipoprotein subtypes. The frequency of one variant of the apoE gene, the APO E  $\epsilon$ 4 allele, is increased in patients with IBM compared with the general population. This unconfirmed result in a small population suggests that the APO E  $\epsilon$ 4 allele may be a predisposing factor for the development of IBM [55].

### Future approaches for the investigation of genetic risk factors in the idiopathic inflammatory myopathies

Many challenges lie ahead in the further definition of genetic risk factors for the IIMs. A common difficulty faced by all researchers assessing the genetic basis of autoimmune diseases is the identification of genes of relatively small effect size, against a background of substantial genetic and environmental variation, using populations often of inadequate size. In addition, specific challenges in identifying genetic risk factors for the myositis syndromes include the rarity and heterogeneity of the IIM, the apparent differences in genetics among the various clinical, serologic, and ethnic groups, and the likely gene-gene interactions that define these diseases. It may be that certain alleles of many polymorphic, physically unlinked genes have been evolutionarily selected to work together as functional units to optimize immune responses to infections and other environmental exposures. If this is the case, then it is possible that some combinations of these polymorphisms may result in abnormal immune responses in certain environments, which could lead to autoimmune disease [56].

As is the case for many other autoimmune diseases, gene-environment interactions also seem to play an important role in the initiation of the IIM. Thus, multidisciplinary approaches which explore the interaction of genetic and environmental factors by integrating a

variety of study designs and take into account the advantages and disadvantages of each, should be considered in future studies [8,44,57,58]. Because it is likely that the heterogeneity of the myositis syndromes reflects varied pathogenic mechanisms in different individuals, it may also be useful to study genotypes in groups of patients classified in new ways. These approaches could include assessing novel IIM phenotypes defined by (1) unique clusters of specific signs, symptoms, and laboratory abnormalities; (2) common patterns of target tissue gene expression using cDNA microarray technology; or (3) different responses to immunomodulating agents.

A major limitation has been the relatively small numbers of subjects within each of the subgroups available for investigation. To address this problem, national and international collaborative efforts have been initiated, and need to be extended, to develop serum and DNA repositories on large populations of well-characterized subjects. This will also allow expansion of these studies to other clinical, serologic and environmental exposure subgroups of myositis that have not yet been studied.

In addition to collaborative efforts to increase population sizes, new technologies and epidemiologic approaches should enhance these efforts [17,59–63]. The human genome project, and its resultant high resolution mapping of MHC and non-MHC regions, may allow an understanding of the true genetic risk factors, rather than those that may only be linked to the true risks. The expanding fields of gene chip and microarray technologies also hold special promise in understanding the pathogenesis of complex disease traits like myositis, inasmuch as the interaction of many different polymorphic gene products can be rapidly assessed in large populations using these methodologies.

In summary, our understanding of the genetics of IIM is in an early stage of development. Many of the current findings in this field are preliminary observations, limited by small samples and weak effect sizes, and should not be considered definitive. The early indications of heterogeneity of genetic risk and protective factors among different serologic and ethnic groups, as well as possible gene-environment interactions, suggest that enhanced understanding in this area should have important diagnostic, therapeutic and preventative implications for improving outcomes of myositis patients in the future.

### Acknowledgments

The authors thank Drs. Steve Bauer, Syed R. Husain, Terrance P. O'Hanlon, and Ms. Uzma Haq for useful comments and assistance during the preparation of this manuscript.

The opinions expressed in this paper are those of the authors and not necessarily those of the Center for Biologics Evaluation and Research or the Food and Drug Administration.

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