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Immunoglobulin Gene Polymorphisms are Susceptibility Factors for Clinical and Autoantibody Subgroups of the Idiopathic Inflammatory Myopathies

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Abstract

Objective—To investigate possible associations of GM and KM markers in European Americans (EA) and African Americans (AA) with adult and juvenile forms of the idiopathic inflammatory myopathies (IIM).

Methods—We performed serologic analyses of polymorphic determinants associated with immunoglobulin gamma heavy (GM) and kappa light chains (KM) in large populations of EA (n=514: 297 adults and 217 juveniles) and AA IIM patients (n=109: 73 adults and 50 juveniles) representing the major clinicopathologic and autoantibody groups.

Results—For EA dermatomyositis (DM) patients, the GM 3 23 5,13 phenotype was a risk factor for both adults (OR=2.2; Pc=0.020) and juveniles (OR=2.2; Pc=0.0013). Of interest, the GM 13 allotype was a risk factor for juvenile DM (JDM) for both EA (OR=3.9; Pc<0.0001) and AA (OR=4.8; Pc=0.033). However, the GM 1,3,17 5,13,21 phenotype was a risk factor for JDM in EA but not in AA. Among the IIM autoantibody groups, GM 3 23 5,13 was a risk factor for EA adults with anti-Jo-1 autoantibodies (OR=3.4; Pc=0.0031), while the GM 3 allotype was protective for adults with anti-threonyl tRNA synthetase or anti-RNP autoantibodies (OR=0.1; Pc=0.047 and OR=0.2;

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Pc=0.034, respectively). In contrast, GM 6 was a risk factor for AA adults with anti-SRP autoantibodies (OR=7.5; Pc=0.041).

Conclusions—These data suggest that polymorphic alleles of GM and KM loci are differentially associated with IIM subgroups defined by age, ethnicity, clinical features and autoantibodies, and expand the list of immune response genes possibly important in the pathogenesis of myositis.

The idiopathic inflammatory myopathies (IIM) are a group of heterogeneous, systemic autoimmune syndromes with shared features of muscle weakness and inflammation of unknown cause (1). IIM patients are characterized by symmetric, proximal muscle weakness, elevated serum levels of muscle enzymes, characteristic myopathic changes on electromyography and inflammatory features on muscle biopsy. The two major clinicopathologic groups of IIM, dermatomyositis (DM) and polymyositis (PM), are distinguished clinically by the presence of photosensitive, pathognomonic rashes in DM. IIM syndromes can be divided further into multiple serologic groups based upon the presence of myositis-specific (MSA) and myositis-associated autoantibodies (MAA), which are often associated with different epidemiologic, clinical, prognostic and immunogenetic features (1, 2{O'Hanlon, 2006 #103)}.

The IIM, like other human autoimmune diseases, likely result from chronic immune activation in genetically susceptible individuals following specific environmental exposures. An immune-mediated etiology in myositis is supported by immunogenetic associations with IIM, the frequent finding of autoantibodies that sometimes correlate in titer with disease activity, the immunopathology in affected tissues and clinical responses to immune-modulating agents (1,3–6). Multiple polymorphic, immune response genes have been associated with the IIM. Most prominent among these are genes encoding antigen-presenting molecules of the human major histocompatibility complex (HLA-A, -B, -Cw, -DR, -DQ, -DP) and other genes which play important regulatory roles in immune activation (e.g., TNFα, IL-1α, IL-1β, IL-1RN and IgG and IgK constant gene polymorphisms) (7,8).

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 (9). For the IIM, GM and KM associations have been described in both Mesoamerican and Korean populations (10,11). 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 (12–18). In an effort to understand if these immune response genes may be important in the pathogenesis of myositis, we have performed a comprehensive examination of GM and KM markers in a large population of European American (EA) (n=514) and African American (AA) (n= 123) adult and juvenile IIM patients representing the major clinicopathologic and autoantibody subgroups.

Patients and Methods

Study subjects

EA and AA adult onset (age of onset ≥ 18 years; n=297 and 73, respectively) and childhood-onset (n=217 and 50, respectively) myositis cases and healthy, unrelated, ethnically-matched controls (n=233 EA and 109 AA) were identified for this study from subjects referred to protocols involving the pathogenesis and treatment of myositis at the NIH Warren Grant Magnuson Clinical Center and the U.S. Food and Drug Administration between 1983 and 2002. Control subjects were obtained from volunteer, blood donors at the NIH Clinical Center in

Bethesda, MD. All subjects were enrolled in investigational review board-approved clinical protocols. Patients were defined as those meeting criteria for probable or definite PM or DM (19) or inclusion body myositis (IBM) (2) and required the exclusion of inherited, metabolic, or infectious myopathies and other causes of muscle disease. Patients who were receiving intravenous gammaglobulin therapy at the time of sample collection were excluded to prevent confounding of GM and KM serotyping. Juvenile onset cases (EA: 19 JPM and 198 JDM; AA: 14 JPM and 36 JDM) came from contributors in the Childhood Myositis Heterogeneity Study Group (see Appendix) and of these, 12 EA and 9 AA had myositis overlapping with another autoimmune disease (CTM), which was defined when patients met probable or definite criteria for myositis and also criteria for another defined autoimmune disease. Among adult patients, 43 EA and 17 AA had CTM (the IIM clinical subgroups of two EA CTM patients were undefined). Data from some of the adult EA subjects have been published in prior studies (10,11).

Laboratory Procedures and Statistical Analyses

GM and KM allotyping was performed using standard hemagglutination inhibition methods to type for IgG1m (1/a, 2/x, 3/f, 17/z), IgG2m (23/n), and IgG3m (5/b1, 6/c3, 13/b3, 21/g) and IgKM 1 and IgKm(3) (20). Myositis-specific (anti-synthetase, anti-signal recognition particle [SRP], anti-Mi-2) and myositis-associated (anti-Ku, -La, -Ro, -RNP, -PM/Scl) autoantibodies were identified in serum samples using previously validated methods of protein and RNA immunoprecipitation and double immunodiffusion (21,22).

Analyses were performed using the SAS(R) System for Windows, version 8.02 (SAS Institute, Cary, NC) as described previously (23). Fisher's Exact P values were adjusted for multiple testing within race and age group for each set of comparisons using the sequential Holm procedure (PROC MULTTEST in SAS); a nonparametric step-down adjustment that controls for family-wise error rates in making no assumptions concerning the correlation structure of the data or the observed P values (24). We defined P values as significant when the corrected P values (Pc) were at or below the 0.05 level. The size of the family (k value) within which the Holm procedure was applied varied by the number of testable factors in each group of comparisons. K family values for multiple GM and KM allotype and phenotype testing were 11 and 13, respectively.

Results

Study Population Overview

The frequencies of IIM clinicopathologic and myositis autoantibody groups seen in EA and AA IIM patients surveyed for GM and KM markers are summarized in Table 1. The distribution of patients in myositis clinical and autoantibody groups was similar as seen in prior studies (2)(5,6,23,24). For adults, as observed previously, IBM was significantly less frequent in AA compared to EA patients (6). Anti-synthetase autoantibodies were the most frequent MSAs detected in all groups with anti-Jo-1 autoantibodies being the most prevalent. DM was the most prevalent clinicopathologic group among juveniles (91% EA and 72% AA JIIM patients) in contrast to adults where DM comprised approximately 38% of both EA and AA cases. Autoantibodies were detected less frequently in EA JIIM as described previously (6,24). In all groups, the majority of patients with anti-Mi-2 autoantibodies had DM while anti-SRP autoantibodies were more prevalent among PM patients and those of AA ethnicity. Higher frequencies of anti-Ro autoantibodies were observed among adult EA and AA patients (11.3% and 15.9%, respectively) as well as AA juveniles (12.5%). Anti-PM/Scl autoantibodies were detected more frequently among EA compared to AA patients (11.3% and 2.9%, respectively) while conversely AA had higher frequencies of anti-RNP autoantibodies (EA, 5.1%: AA, 15.5%).

GM and KM Associations with IIM Clinicopathologic and Myositis Autoantibody (MSA and MAA) Groups

A number of GM and KM markers were found to be significant risk factors (Pc < 0.05 after correction for multiple comparisons) for different clinicopathologic groups of EA and AA IIM patients (Table 2). KM 1 and GM 13 allotypes were observed as risk factors for adult PM (EA) and JDM (EA and AA) patients, respectively. EA subjects with the GM 1,3,17 5,13,21 phenotype were also at increased risk for JDM (OR=2.2; Pc=0.0060). Furthermore, in EA with DM, GM 1,3,17 5,13,21 was significantly more frequent in juvenile compared to adult patients (38% vs. 20%, Pc=0.019). In contrast, the GM 3 23 5,13 phenotype was a significant risk factor for EA DM independent of age. Among AA patients, GM 5 and GM 13 were risk factors for adult IIM and JDM, respectively. However, AA subjects with the KM 1,1 phenotype were at increased risk for JDM in contrast to their EA counterparts.

Because certain immune response genes including GM and KM have been defined as risk or protective factors for different autoantibodies, we assessed GM and KM associations in the IIM after stratifying patients by myositis autoantibodies. As was the case for the clinicopathologic groups, different GM and KM allotypes and phenotypes were found to be significant risk or protective factors for different MSA and MAA groups of EA and AA IIM (Table 2). Among EA, the GM 3 allotype was identified as a protective factor for IIM patients with either anti-threonyl tRNA synthetase (anti-PL-7) or anti-RNP autoantibodies. The GM 3 23 5,13 phenotypic risk factor shared among EA adult and juvenile IIM patients was also associated with EA adults, but not children, producing anti-Jo-1 autoantibodies; however, this distinction is the likely result of infrequent anti-Jo-1 autoantibody detection in EA JDM patients (see Table 1). As was the case in the clinicopathologic groups, the GM and KM allotypes and phenotypes associated with IIM autoantibody groups differed in AA from those seen in EA. In AA adult IIM, GM 6 and KM 1,1 were risk factors for patients with anti-SRP and anti-Ro autoantibodies, respectively..

Comparisons of genetic susceptibility factors between different ethnic and age groups of IIM patients

Together, these findings suggest that different polymorphic alleles of GM and KM loci are associated with various IIM subgroups as stratified by age, ethnicity, clinicopathologic features or autoantibodies (Table 3). For EA DM patients, the GM 3 23 5,13 phenotype was a risk factor shared between adults and juveniles. In contrast, the GM 13 allotypic risk factor associated with JDM clearly segregated those patients from adults in both EA and AA ethnic groups. Moreover, the GM 1,3,17 5,13,21 phenotypic risk factor associated with EA JDM further stratified EA and AA juveniles. Similarly, KM 1 and GM 5, which are risk factors for EA PM and AA IIM in adults, respectively, did not appear to be risk factors in juveniles or adults with DM. Among the myositis autoantibody groups, the EA GM 3 23 5,13 phenotype was a risk factor for anti-Jo-1 autoantibodies in EA adult IIM patients. Other unique observations included the GM 3 protective association with anti-threonyl tRNA synthetase (anti-PL-7) or anti-RNP autoantibodies in EA adult IIM. In contrast, GM 6 was observed as a risk factor for AA adults with anti-SRP autoantibodies.

In addition, to assess for possible epistatic interactions between GM and KM loci, we performed analyses of genetic susceptibility using all possible paired combinations of GM and KM allotypes and phenotypes in IIM and JIIM patients compared to ethnically matched controls. No evidence of GM-KM interactions was detected among AA IIM or JIIM patients. Surprisingly, however, EA patients sharing the GM 13 (a risk factor for JDM) and KM 3 allotypes were at increased risk for disease for both adult (67.7% IIM vs. 50.6% controls, OR=2.0; Pc=0.022) and juvenile IIM (82.0% JIIM vs. 50.6% controls, OR=4.4; Pc<0.0001). Co-detection of GM 13 and KM 1 was also a risk factor for EA adult IIM (32.3% IIM vs. 15.9%

controls, OR=2.5; Pc=0.0036). Among phenotypes, the GM 3 23 5,13 and KM 3,3 combination was a unique risk factor for EA juvenile IIM (42.9% JIIM vs. 24.0% controls, OR=2.4; Pc=0.0068).

Discussion

Previous immunogenetic studies have demonstrated the utility of stratifying the IIM syndromes into more homogeneous subgroups using age, ethnicity, clinicopathologic features, and autoantibodies (2,5,6,23,25,26). Distinct patterns of immunogenetic susceptibility in different groups of IIM patients are clearly evident among some MHC genes (e.g., HLA-A, -B, -Cw, -DRB1 and -DQA1), which remain the strongest and most consistent genetic associations with the IIM and most other autoimmune diseases (5,6,23,25–27). In addition to HLA factors, polymorphic immune response genes mapping both within the MHC and on other chromosomes have been identified as risk and protective factors for IIM (7,8,28,29). It is hypothesized that the presence and complex interplay of multiple, polymorphic genes predisposing to disease, along with the absence of genes protecting from disease -- in combination with the necessary and sufficient environmental exposures -- is responsible for the wide spectrum of phenotypic and pathogenetic variants associated with a particular autoimmune pathology (30).

Allelic variants of the constant domain of immunoglobulin gamma heavy chains (GM) and kappa light chains (KM) are associated with differential immune responses to a variety of infectious disease agents, vaccines, and a host of other immune-mediated and autoimmune diseases (12–18,31). For the IIM, our laboratory has previously identified GM and KM susceptibility factors in both Korean and Mesoamerican populations, although we were unable to detect significant associations in a smaller group (n=118) of adult EA patients (10,11). In the present study, however, the increased statistical power associated with a larger sample size of adult EA IIM patients has enabled our identification of several significant GM and KM allotypic and phenotypic associations. Moreover, although statistical power is still limited in the smaller subgroups, we observed that these and other GM and KM susceptibility factors differed in EA and AA ethnic groups as well as adult and juvenile forms of the IIM. While the GM 3 23 5,13 phenotype was shared between EA DM and JDM, several additional markers were detected exclusively among JDM patients (GM 13 and GM 1,3,17 5,13,21). Interestingly, the GM 13 risk factor was also identified trans-ethnically among EA and AA JDM while the GM 1,3,17 5,13,21 risk factor was observed previously among Mesoamericans with IIM (10). Among IIM patients with different clinical and autoantibody groups, other markers clearly differentiated EA and AA ethnic groups including the GM 5 and GM 6 allotypes which were unique susceptibility factors for AA IIM and those AA patients producing anti-SRP autoantibodies, respectively.

Associations among polymorphic GM and KM determinants and different autoantibodies have been reported for other connective tissue diseases. In EA, GM 1,3,17 23 5,13,21/KM 1,3 and GM 3 23 5,13/KM 3,3 phenotypes were associated with the presence or absence of anti-fibrillin-1 autoantibodies in systemic sclerosis patients (15). In contrast, anti-fibrillin-1 autoantibody production was associated with KM 3,3 in AA. An association between native type II collagen autoantibodies and GM 1,3,17 23 5,21 was identified also among rheumatoid arthritis patients from the United Kingdom (32).

Our examination of possible epistatic or gene-gene interactions identified allotypic and phenotypic variants that when combined resulted in significant risk among EA IIM patients. Most notably, the GM 13 risk factor - found associated exclusively with JDM in univariate analyses - was also identified as a risk factor for adult EA IIM when in combination with either the KM 1 or KM 3 allotypes. The biologic plausibility of mechanistic interactions between

physically unlinked loci is becoming increasing recognized in a number of disease states and other biological systems (33). Of interest, another study has identified possible interactions of GM and KM loci in hepatitis C-infected patients producing autoantibodies to LKM1 (12). Whether the GM and KM interactions identified in our study are simply additive effects or representative of biologically relevant interactions is still unclear. These data suggest, however, that different GM and/or KM variants likely contribute, at least in part, to the diverse pathogenetic mechanisms associated with the IIM and other connective tissue diseases.

Several hypotheses may possibly explain the biologic basis for the association of immunoglobulin constant region polymorphisms in humoral immunity and immune-mediated disease. GM and KM markers may be in linkage disequilibrium with immunoglobulin variable region genes on extended haplotypes that modulate the expression of different IgG subclasses. In fact, serum concentrations of the various IgG subclasses have been associated with particular GM and KM markers in different ethnic groups (34). (35). Differences in serum IgG subclass concentrations may affect binding and activation of cognate Fc receptors and thus modulate various immunoregulatory and/or effector pathways. Polymorphic determinants of Ig constant domains have also been demonstrated to influence antibody binding affinities directly (31).

The detection of shared and distinctive GM and KM susceptibility factors for the IIM, along with previously defined HLA and cytokine alleles among multiple ethno-geographic populations, may help explain the phenotypic heterogeneity generally associated with these and other connective tissue diseases (5,6,10,11,23,25,26,28). More specifically, these and other studies suggest that the differential expression of polymorphic risk and protective determinants, as influenced by ethnicity and environmental exposures, likely affect the age of disease onset, clinicopathologic features, and autoantibody responses, which collectively comprise the IIM syndromes.

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Table 1

Clinicopathologic and Autoantibody Groups of European American (EA) and African American (AA) Patients with Idiopathic Inflammatory Myopathies (IIM)*

			Clinical Composition N (%)							
	IIM N (%)		PM		DM		IBM		JIIM¶	
	EA N=297	AA N=73	EA N=149	AA N=43	EA N=114	AA N=27	EA N=32	AA N=3	EA N=217	AA N=50
Myositis-Specific Autoantibodies (MSA)										
All MSA	91 (33.2)	41 (59.4)	52 (37.1)	25 (62.5)	39 (37.9)	18 (66.7)	0 (0.0)	0 (0.0)	7 (4.5)	10 (31.2)
Anti-Synthetases	72 (26.2)	26 (37.7)	45 (32.1)	13 (32.5)	27 (26.2)	15 (55.6)	0 (0.0)	0 (0.0)	5 (3.2)	4 (12.5)
Anti-Jo-1	50 (18.2)	15 (21.7)	32 (22.8)	7 (17.5)	18 (17.5)	8 (29.6)	0 (0.0)	0 (0.0)	4 (2.3)	3 (94)
Anti-PL-7	7 (2.6)	4 (5.8)	5 (3.6)	3 (7.5)	2 (1.9)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-PL-12	4 (1.4)	3 (4.3)	3 (2.1)	2 (5.0)	4 (3.9)	1 (3.7)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.1)
Anti-OJ	5 (1.8)	1 (1.4)	3 (2.1)	0 (0.0)	2 (1.9)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-EJ	3 (1.1)	3 (4.3)	2 (1.4)	1 (2.5)	1 (1.0)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-Mi-2	13 (4.7)	4 (5.8)	1 (0.7)	1 (2.5)	12 (11.6)	3 (11.1)	0 (0.0)	0 (0.0)	1 (0.6)	2 (6.3)
Anti-SRP	6 (2.2)	11 (15.9)	6 (4.3)	11 (27.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	4 (12.5)
Negative†	183 (66.8)	28 (40.6)	88 (62.8)	15 (37.5)	64 (62.1)	11 (40.7)	29 (100.0)	2 (100.0)	147 (95.4)	22 (68.8)
Myositis-Associated Autoantibodies (MAA)										
All MAA	92 (33.6)	26 (37.7)	48 (34.3)	14 (35.0)	34 (33.0)	12 (44.4)	8 (27.6)	0 (0.0)	20 (13.0)	12 (37.5)
Anti-PM/Scl	31 (11.3)	2 (2.9)	16 (11.4)	2 (5.0)	15 (14.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (6.5)	0 (0.0)
Anti-Ro	31 (11.3)	11 (15.9)	15 (10.7)	7 (17.5)	10 (9.7)	4 (14.8)	5 (17.2)	0 (0.0)	3 (1.9)	4 (12.5)
Anti-La	13 (4.7)	3 (4.3)	5 (3.6)	1 (2.5)	4 (3.9)	2 (7.4)	3 (10.3)	0 (0.0)	1 (0.6)	1 (3.1)
Anti-U-RNP	14 (5.1)	10 (14.5)	9 (6.4)	4 (10.0)	5 (4.8)	6 (22.2)	0 (0.0)	0 (0.0)	6 (3.9)	7 (21.9)
Anti-Ku	3 (1.1)	0 (0.0)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0)	0 (0.0)
Negative†	198 (72.3)	51 (73.9)	99 (70.7)	28 (70.0)	75 (72.8)	21 (77.8)	23 (79.3)	2 (100.0)	138 (89.6)	26 (81.2)

*Abbreviations: PM, polymyositis; DM, dermatomyositis; IBM, inclusion body myositis; Anti-synthetases include anti-Jo-1 (anti-histidyl-tRNA synthetase), anti-PL-7 (anti-threonyl-tRNA synthetase), anti-PL-12 (anti-alanyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase) and anti-EJ (anti-glycyl-tRNA synthetase). Autoantibody data were available for EA: 152/168 PM, 245/312 DM, 29/32 IBM; AA: 49/57 PM, 50/63 DM, 2/3 IBM.

¶JIIM (EA: 19 PM, 198 DM; AA: 14 PM, 36 DM)

†Negative for serum autoantibodies evaluated in this study (see Methods).

Table 2

Immunogenetic differences between different clinicopathologic and autoantibody groups of European American (EA) and African American (AA) IIM patients and unrelated, ethnically-matched controls*

EA	GM/KM Marker	Cases% (n/N†)	Controls% (n/N†)	P	Pc	OR	95% CI
ALLOTYPES							
Adults		**PM**					
	KM 1	41.6 (62/149)	26.1 (60/230)	0.0023	0.025	2.0	1.27–3.21
		THR-IIM					
	GM 3	*42.9 (3/7)*	*89.6 (207/231)*	*0.0043*	*0.047*	*0.1*	*0.01–0.56*
		RNP-IIM					
	GM 3	*57.1 (8/14)*	*89.6 (207/231)*	*0.0031*	*0.034*	*0.2*	*0.04–0.60*
Juveniles		**JDM**					
	GM 13	87.9 (174/198)	65.2 (135/207)	<0.0001	<0.0001	3.9	2.26–6.76
PHENOTYPES							
Adults		**DM**					
	Gm 3 23 5,13	59.6 (68/114)	40.7 (83/204)	0.0015	0.020	2.2	1.32–3.54
		JO1-IIM					
	GM 3 23 5,13	70.0 (35/50)	40.7 (83/204)	0.0002	0.0031	3.4	1.68–7.12
Juveniles		**JDM**					
	Gm 1,3,17 5,13,21	37.9 (75/198)	22.0 (45/205)	0.0005	0.0060	2.2	1.37–3.45
	Gm 3 23 5,13	60.1 (119/198)	40.7 (83/204)	0.0001	0.0013	2.2	1.45–3.34
AA		**Cases% (n/N†)**	**Controls% (n/N†)**	**P**	**Pc**	**OR**	**95% CI**
ALLOTYPES							
Adults		**IIM**					
	GM 5	98.6 (72/73)	85.3 (93/109)	0.0016	0.018	12.4	1.82–526.5
		SRP-IIM					
	GM 6	54.5 (6/11)	13.8 (15/109)	0.0037	0.041	7.5	1.64–34.6
Juveniles		**JDM**					
	GM 13	88.9 (32/36)	62.6 (62/99)	0.0030	0.033	4.8	1.50–19.9
PHENOTYPES							
Juveniles		**JDM**					

EA	GM/KM Marker	Cases% (n/N†)	Controls% (n/N†)	P	Pc	OR	95% CI
	KM 1,1	27.8 (10/36)	7.3 (8/109)	0.0028	0.037	4.8	1.53–15.5
	RO-IIM						
	KM 1,1	75.0 (3/4)	7.3 (8/109)	0.0027	0.032	37.9	2.5–2005.7

*Abbreviations: PM, polymyositis; (J)DM, (juvenile)dermatomyositis; MSA, myositis-specific autoantibody; MAA, myositis-associated autoantibody; THR, anti-threonyl tRNA synthetase autoantibodies; RNP, anti-ribonucleoprotein autoantibodies; JO1, anti-histidyl tRNA synthetase autoantibodies; SRP, anti-signal recognition particle autoantibodies; P, P values; Pc, corrected P values; OR, odds ratio; 95% CI, confidence interval. Other abbreviations per Table 1. Markers identified as *protective* factors are listed in italics.

†The number (n) of sero-marker positive subjects/the total number of subjects (N) for which complete sero-typing data were available for a given marker.

Fisher's Exact P values were adjusted for multiple testing within race and age group for each set of comparisons using the sequential Holm procedure as described in Methods. The size of the family (k value) within which the Holm procedure was applied varied by the number of testable factors in each group of comparisons (k family values for multiple GM and KM allotype and phenotype testing were 11 and 13, respectively).

Table 3

Summary of Significant GM and KM Associations (allotype/phenotype) in Different IIM Clinical and Autoantibody Groups.*

		EA		AA	
Clinicopathologic Groups		**Adult**	**Juvenile**	**Adult†**	**Juvenile**
PM	(allotype)	KM 1			
DM	(allotype)		GM 13		GM 13
	(phenotype)	GM 3 23 5,13	GM 3 23 5,13		KM 1,1
			GM 1,3,17 5,13,21		
Myositis Autoantibody Groups					
IIM MSA:					
	anti-Jo-1 (phenotype)	GM 3 23	5,13		
	anti-PL-7 (allotype)	*GM 3*			
	anti-SRP (allotype)			GM 6	
IIM MAA:					
	anti-RNP (allotype)	*GM 3*			
	anti-Ro (phenotype)				KM 1,1

*Abbreviations: per Tables 1 - 2. Markers identified as *protective* factors are listed in italics. All clinical and autoantibody subgroups were examined for GM and KM associations and a blank notation in that column means no significant associations were found.

†The GM 5 allotype was also identified as a risk factor for adult AA IIM patients.