

Differences in Idiopathic Inflammatory Myopathy Phenotypes and Genotypes Between Mesoamerican Mestizos and North American Caucasians

Ethnogeographic Influences in the Genetics and Clinical Expression of Myositis

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Objective. As part of a larger, worldwide study of the ethnogeography of myositis, we evaluated the clinical, serologic, and immunogenetic features of Mestizo (Mexican and Guatemalan) and North American Cau-

casian patients with idiopathic inflammatory myopathy (IIM).

Methods. Clinical manifestations, autoantibodies, HLA-DRB1 and DQA1 alleles, and immunoglobulin Gm/Km allotypes were compared between 138 Mestizos with IIM and 287 Caucasians with IIM, using the same classification criteria and standardized questionnaires.

Results. IIM in Mestizo patients was characterized by a higher proportion of dermatomyositis (69% of adult Mestizos versus 35% of adult Caucasians; $P < 0.001$) and anti-Mi-2 autoantibodies (30% versus 7% of adults, respectively, and 32% versus 4% of children, respectively; $P < 0.01$). Genetic risk factors also differed in these populations. Whereas Mestizos had no HLA risk factors for IIM, HLA-DRB1*0301, the linked allele DQA1*0501, and DRB1 alleles sharing the first hyper-variable region motif ⁹EYSTS¹³ were major risk factors in Caucasian patients with IIM. Furthermore, different HLA-DRB1 and DQA1 alleles were associated with anti-Mi-2 autoantibodies (DRB1*04 and DQA1*03 in Mestizos and DRB1*07 and DQA1*02 in Caucasians). Immunoglobulin γ -chain allotypes Gm(1), Gm(17) (odds ratio for both 11.3, $P = 0.008$), and Gm(21) (odds ratio 7.3, $P = 0.005$) and κ -chain allotype Km(3) (odds ratio 7.3, $P = 0.005$) were risk factors for IIM in Mestizos; however, no Gm or Km allotypes were risk or protective factors in Caucasians. In addition, Gm and Km phenotypes were unique risk factors (Gm 1,3,17 5,13,21 and Gm 1,17 23 21 and Km 3,3) or protective factors (Km 1,1) for the development of myositis and

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anti-Mi-2 autoantibodies (Gm 1,2,3,17 23 5,13,21) in adult Mestizos.

Conclusion. IIM in Mesoamerican Mestizos differs from IIM in North American Caucasians in the frequency of phenotypic features and in the immune-response genes predisposing to and protecting from myositis and anti-Mi-2 autoantibodies at 4 chromosomal loci. These and other data suggest the likelihood that the expression of IIM is modulated by different genes and environmental exposures around the world.

Autoimmune diseases are acquired conditions that appear to result from environmental exposures in genetically susceptible individuals (1). Although only a few environmental risk factors for autoimmunity have been identified (2), a growing number of genetic risk factors are being associated with autoimmune disorders. The major known genetic risk factors are the polymorphic genes in the major histocompatibility complex (MHC) region of chromosome 6, particularly the HLA class II alleles (3). Genes encoding serologic markers on the IgG heavy chains (located on chromosome 14) and on κ light chains (located on chromosome 2), known as Gm and Km allotypes, respectively, are also genetic risk factors for certain autoimmune diseases (4).

The naturally occurring variation in the genetics of human populations, which has likely occurred because of founder effects (5) and environmental selection in geographically isolated locations (6), allows an opportunity to assess possible differences in phenotypes and risk factors for autoimmune diseases on a global basis. These studies may allow insight into the pathogenesis of autoimmunity and understanding of whether different mechanisms may lead to a common phenotype. Such studies have resulted in the finding of similar clinical presentations and genetic risk factors for certain diseases in some ethnogeographic populations, but different genotypes and phenotypes in other populations (7–10). Possible explanations for the differences in phenotypes and genotypes for the same autoimmune disease in different locations include different pathogeneses, different combinations of multiple genetic risk factors, and/or different environmental triggers, which may result in unique gene–environment interactions that lead to development of the disease (11).

The idiopathic inflammatory myopathies (IIM) are a group of rare systemic diseases that are thought to have an immune-mediated component and whose hallmark is chronic muscle inflammation, resulting in muscle weakness (12). The IIM can be classified into the clinicopathologic groups dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM), as

well as into serologic groups based on the presence of myositis-specific autoantibodies (MSA), which differ in clinical presentation, season of onset, genetics, and prognosis (13,14). Similar to other autoimmune disorders, there appears to be a genetic as well as an environmental component in the pathogenesis of the IIM (15). Little information is available regarding the environmental agents that may result in myositis (16); however, MHC and non-MHC genetic risk and protective factors have been identified (17). Of the genes studied to date, HLA-DRB1*0301 and the linked DQA1*0501 allele are the strongest genetic risk factors for myositis in Caucasians, for both the adult and juvenile forms (18,19). Alleles of other polymorphic genes, including those encoding the tumor necrosis factor α promoter and interleukin-1 receptor antagonist, have also been shown to be risk factors in juvenile patients with IIM (20,21).

As part of a larger effort by an international group of myositis specialists to explore global differences in phenotypes and risk factors for the development of IIM, we compared clinical, serologic, and immunogenetic features in Mesoamerican Mestizo and North American Caucasian patients with IIM.

PATIENTS AND METHODS

Patients. From 1987 to 2000, 138 consecutive Mesoamerican IIM patients (99 females and 39 males; 40 with IIM onset at <18 years of age [juvenile IIM] and 98 with adult-onset IIM) who met the criteria for probable or definite IIM (13,22) were enrolled into this study by the members of the International Myositis Collaborative Study Group from referral centers in Guatemala City, Guatemala and from Mexico City and Guadalajara, Mexico. These patients were all ethnically self-classified as Mestizos and geographically classified as Mesoamericans. From 1985 to 2000, 290 consecutive, ethnically self-classified Caucasian North American patients with IIM (181 females and 109 males; 287 with IIM of adult onset and 3 with juvenile onset) who met the same criteria (13,22) were enrolled into epidemiologic protocols at the National Institutes of Health and at the Food and Drug Administration. Physicians and patients/parents completed standardized clinical questionnaires, and patients donated blood samples that were frozen for later use (13).

Controls. For the assessment of risk factors in IIM, unrelated, race-matched healthy volunteers without a known genetic or autoimmune disease served as controls. The Mestizo controls used for HLA studies ($n = 99$) were from the Instituto Nacional de la Nutrición, Mexico City, Mexico. The HLA distribution in these controls was similar to that in other published Mestizo groups (23). The Mestizo controls used for Gm/Km allotype and phenotype studies were from the same location in Mexico ($n = 38$) and from Guadalajara ($n = 95$). Healthy blood donors and normal volunteers from throughout the United States served as controls for the studies of HLA ($n = 99$) and Gm/Km ($n = 133$) in Caucasians.

Laboratory methods. HLA typing. Alleles at the DRB1 (n = 289) and DQA1 (n = 21) loci were determined by previously described standardized and validated molecular typing techniques (24,25).

Gm and Km allotyping. Standard hemagglutination-inhibition methods were used to type for G1m(1/a,2/x,3/f,17/z), G2m(23/n), and G3m(5/b1,6/c3,13/b3,21/g) and Km(1,3) (26). The 9 Gm allotypes present were found in 35 phenotypic combinations in Caucasian patients and 10 phenotypic combinations in Mesoamericans. Km allotypes could not be determined in 5 Mestizo IIM patients, and they were excluded from the allotype and phenotype comparisons.

Autoantibody studies. MSA (antisyntetase, anti-signal recognition particle [anti-SRP], and anti-Mi-2 autoantibodies) were identified using previously validated methods of protein and RNA immunoprecipitation and double immunodiffusion (13,27).

Statistical analysis. GraphPad InStat (San Diego, CA), EpiInfo (Centers for Disease Control and Prevention, Atlanta, GA), and SAS (Cary, NC) software were used for all statistical analyses. P values were calculated by chi-square analysis or Fisher's exact tests using a 2 × 2 contingency table. P values were deemed significant based on the family-wise error rate of 0.05. Corrections for multiple comparisons were made using the Holm procedure (28), and only significant adjusted P values are reported. Because of the small number of Caucasian juvenile IIM patients enrolled in this study (n = 3), they were excluded from the analyses, and comparisons of the Mestizo juvenile IIM patients were made with published data on Caucasian juvenile IIM patients (29,30). Because adult and pediatric IIM patients differ in the distributions of clinical groups, manifestations, and frequency of autoantibodies but are not known to differ in genetic risk factors, we assessed children separately from adults for the clinical and serologic comparisons.

RESULTS

Clinical groups and demographics. The distribution of clinical groups among the adult Mesoamerican IIM patients differed significantly (P < 0.001 by a single chi-square test on a 5 × 2 table) from that among the adult Caucasian patients (Table 1). Mestizos had a higher frequency of DM, but IBM and cancer-associated myositis (CAM) were absent. In adults, the ratios of females to males (3.3 to 1 in Mestizos versus 2.1 to 1 in Caucasians) and the ages at myositis onset (18–74 years [mean 39.7 years] in Mestizos versus 18–73 years [mean 41.4 years] in Caucasians) were similar in the 2 IIM populations. The higher frequency of DM was detected in the Mestizo IIM cohort whether all patients were analyzed together (i.e., combined Mestizo adults and children) or the Mesoamerican adult IIM patients were compared with the Caucasian adult IIM patients.

To avoid possible confounding in the analyses of the clinical and serologic groups, which are known to

Table 1. Comparison of selected features of Mesoamerican and US Caucasian adult populations of patients with idiopathic inflammatory myopathy (IIM)*

Feature	Mesoamerican Mestizo adult IIM	US Caucasian adult IIM
Clinical group	(n = 98)	(n = 287)
PM	27	36
DM	69†	35
IBM	0†	13
CTM	4	9
CAM	0‡	7
Serologic group	(n = 87)	(n = 287)
Antisyntetase	5†	28
Anti-Mi-2	30†	7
Anti-SRP	1	2
No MSA (MSA-negative)	64	62
Clinical feature	(n = 93)	(n = 98)
Fever	35	45
Raynaud's phenomenon	32	44
Arthritis	29§	51
Distal weakness	29§	10
Asymmetric weakness	11	7
Muscle atrophy	36†	6
Episodes of falling	40†	7
Carpal tunnel syndrome	14	26
Interstitial lung disease	12§	30
Palpitations	23	17
Dysphagia	60	47
V-sign	54†	20
Shawl sign	21	13
Cuticular overgrowth	14	21

* Except where otherwise indicated, values are the percentage of the population. The significant differences noted are after correction for multiple comparisons. PM = polymyositis; DM = dermatomyositis; IBM = inclusion body myositis; CTM = another defined connective tissue disease and myositis in an overlap syndrome; CAM = cancer-associated myositis; anti-SRP = anti-signal recognition particle; MSA = myositis-specific autoantibodies.

† P < 0.001 versus Caucasians.

‡ P < 0.005 versus Caucasians.

§ P < 0.01 versus Caucasians.

differ in frequency in adults and children, we compared Mesoamerican adult IIM patients with Caucasian adult patients and Mesoamerican juveniles with published data on Caucasian juvenile patients. In the Mestizo juvenile IIM population, DM cases far outnumbered PM cases (only 2 of 40 juvenile IIM patients had PM, so that 95% had DM), which is similar to the published distribution among US juvenile IIM populations (86–95% with DM) (29,30). In Mesoamerican children, the ages at myositis onset (3–17 years [mean 10.4 years] in Mestizos versus 1.2–17 years [mean 5.4–6.9 years] in published reports on Caucasians [29,30]) and the female-to-male ratio (1.5 to 1 in Mestizos versus 2.1 to 1 in published Caucasian populations) did not differ significantly from those in North American children.

Serologic and clinical features. Consistent with the higher frequency of DM in the Mesoamerican patients, the prevalence of certain autoantibodies and clinical manifestations differed between the groups (Table 1). Antisynthetase autoantibodies were less frequent (5% versus 28%), but DM-associated anti-Mi-2 autoantibodies were more frequent (30% versus 7%), in the Mestizo adults compared with the Caucasian adults. Anti-SRP autoantibodies were relatively rare in both groups. Juvenile IIM patients from Mesoamerica were similar to the adults, in that anti-Mi-2 autoantibodies were the most commonly seen MSA and were more frequent than those reported in North American juvenile IIM patients (8 of 25 Mestizo children tested [32%] were anti-Mi-2 autoantibody positive versus 4% of North American children; $P < 0.01$) (30). The proportions of patients who were MSA negative were similar in both adult and juvenile Mesoamerican IIM patients (64% of adults and 64% of children), but differed between Mestizo and North American children (64% versus 95%; $P = 0.002$) (30).

The prevalence of certain clinical manifestations also differed in Mesoamerican IIM patients and US Caucasian IIM patients. Mesoamerican adults had significantly higher frequencies of distal weakness, muscle atrophy, episodes of falling, and V-sign rash, and lower frequencies of arthritis and interstitial lung disease than did North American Caucasian IIM patients (Table 1). Similar results were seen when comparing only the adult patients with DM in the 2 populations; we found a higher frequency of distal weakness in the Mesoamerican DM patients than in the Caucasian DM patients (34% versus 10%; $P = 0.005$), as well as muscle atrophy (38% versus 2%; $P < 0.001$), episodes of falling (38% versus 7%; $P < 0.001$), and V-sign rash (69% versus 33%; $P < 0.001$), but less interstitial lung disease in the Mestizo DM group (6% versus 32% in Caucasians; $P = 0.001$). It is possible that a longer delay in diagnosis and a further delay in the subsequent initiation of therapy in the Mesoamericans compared with the Caucasians may have led to the higher frequencies of distal weakness, episodes of falling, and muscle atrophy in the Mestizos.

Although V-sign and shawl sign rashes and cuticular overgrowth have been associated with anti-Mi-2 autoantibodies in Caucasian DM patients (13), these manifestations were not found to be significantly associated with anti-Mi-2 autoantibodies in Mestizo IIM patients. It is notable that no significant differences in clinical manifestations were seen between Mesoamerican patients who had anti-Mi-2 autoantibodies and those lacking this autoantibody in adults, in children, or in the combined group (data not shown).

The only clinical difference between adult and juvenile DM patients was a lower frequency of V-sign rash in the Mestizo juvenile DM patients (69% of adults versus 30% of children; $P < 0.0001$), despite the same frequency of anti-Mi-2-positive patients in both groups (data not shown). No other significant differences in clinical features were present between adults and children overall or in comparisons of any clinical or serologic subset of patients.

Genetics. The strongest known risk factors for myositis in Caucasians are HLA-DRB1*0301, the linked allele DQA1*0501, and DRB1 alleles sharing the first hypervariable region motif ⁹EYSTS¹³ (18). These were confirmed as risk factors in US Caucasian patients (all $P < 0.001$; data not shown), but none of these genetic components were found to be risk factors in the total myositis population of Mesoamericans (Table 2). Although no HLA risk or protective factors were present in the total Mestizo IIM population, several were identified among the serologic groups. The development of anti-Mi-2 autoantibodies in both Mestizo and Caucasian adult IIM patients was associated with DRB1*0701. HLA-DRB1*0701 was seen in 58% of adult Mestizo anti-Mi-2-positive patients (data not shown) versus 21% of Mestizo controls ($P < 0.001$) and in 88% of adult Caucasian anti-Mi-2-positive patients versus 24% of Caucasian controls ($P < 0.0001$). HLA-DQA1*0201, which is in linkage disequilibrium with DRB1*0701, was associated with the development of anti-Mi-2 autoantibodies in Caucasians only (86% versus 23% of healthy controls; $P < 0.0001$) as previously described (31), whereas HLA-DRB1*04 and HLA-DQA1*03 were identified as unique risk factors for the development of anti-Mi-2 autoantibodies in Mestizos (Table 2). When Mestizo IIM patients were segregated by age at onset, DRB1*0701 and DQA1*03 were risk factors for the development of anti-Mi-2 autoantibodies in adults, but surprisingly, not in children, although DNA for molecular HLA typing was available from only 8 anti-Mi-2-positive juvenile IIM Mesoamerican patients.

In contrast to Caucasians, in whom no Gm or Km risk or protective factors for IIM were seen (Table 3), Gm/Km allotype and phenotype risk and protective factors were found in both adult and juvenile Mesoamerican IIM patients. Gm(1) and Gm(17) (which were linked in all Mestizo IIM patients) and Gm(21) were each identified as risk factors for myositis in Mestizos (Table 4). The Gm 1,3,17 5,13,21 phenotype was a risk factor for myositis in the combined total adult

Table 2. Comparison of HLA-DRB1 and DQA1 alleles in Mesoamerican IIM patients and healthy Mesoamerican controls*

HLA allele	Patient subset			Antibody subset		Controls
	All IIM	Adult IIM	Juvenile IIM	All anti-positive Mi-2	All MSA negative	
DRB1	(n = 94)	(n = 73)	(n = 22)	(n = 30)	(n = 54)	(n = 99)
*01	13	15	5	7	15	10
*02	9	11	0	10	11	18
*03	18	12	27	10	19	10
*04	49	48	41	77†	39	41
*07	24	26	14	47	21	21
*08	24	29	11	3	27	27
*09	3	1	11	0	2	2
*10	0	0	0	0	1	1
*11	14	12	18	7	17	17
*12	0	0	0	0	2	2
*13	8	10	5	10	10	10
*14	18	18	14	13	20	20
DQA1	(n = 97)	(n = 74)	(n = 23)	(n = 32)	(n = 53)	(n = 99)
*01	24	27	13	13	30	38
*02	23	24	4	41	13	20
*03	59	54	73	84‡	51	43
*04	27	30	17	13	40	27
*05	48	51	43	31	55	43
*06	2	1	4	0	2	0

* Except where indicated otherwise, values are the percentage of the population. See Table 1 for definitions.
 † Odds ratio 4.7 (95% confidence interval 1.7–13.3), *P* < 0.01 versus controls (adjusted for multiple comparisons).
 ‡ Odds ratio 7.03 (95% confidence interval 2.3–22.8), *P* < 0.001 versus controls (adjusted for multiple comparisons).

and juvenile Mestizo patient population (Table 5). Some Gm phenotypes differed in frequency between adult and juvenile IIM in Mesoamerica, although the number of patients available for study was small. For example, Gm 1,17 23 21 was a risk factor for the development of myositis in adult, but not pediatric, patients, while Gm 1,3,17 5,13,21 was a risk factor for juvenile, but not adult, IIM. Remarkably, Gm 1,2,3,17 23 5,13,21, which was a unique risk factor for the develop-

ment of anti-Mi-2 autoantibodies in adults, was not seen in any of the 8 juvenile patients with anti-Mi-2 autoantibodies in whom Gm/Km were assessed. Furthermore, in IIM patients without an MSA, the Gm 1,3,17 5,13,21 phenotype was a risk factor in juveniles (odds ratio 23.4, 95% confidence interval 3.4–194, *P* < 0.001), but not in adults.

Km allotypes and phenotypes were also unique risk and/or protective factors for Mesoamerican myositis. The Km(3) allotype and Km 3,3 phenotype were risk factors, while Km(1) and Km 1,1 were protective factors, in the Mestizo total IIM population and in adults with anti-Mi-2 autoantibodies (Tables 4 and 5). Although the trends were similar, none of these Km allotypes or phenotypes was a significant risk or protective factor in juvenile patients or in any clinical group (PM or DM). This lack of statistical significance was possibly due to the smaller number of patients available for study in these subgroups.

DISCUSSION

These data, which present the first comprehensive findings on Mesoamerican myositis, strengthen the evidence for differences in clinical manifestations, serologies, and genetic risk and protective factors for IIM around the world. In Mesoamerica, we observed the

Table 3. Comparison of Gm and Km allotypes in US Caucasian IIM patients and healthy Caucasian controls*

Gm or Km allotype	Adult IIM (n = 118)	Controls (n = 216)
Gm(1)	52	55
Gm(2)	21	23
Gm(3)	87	95
Gm(17)	50	55
Gm(23)	51	66
Gm(5)	90	95
Gm(6)	3	3
Gm(13)	90	95
Gm(21)	44	51
Km(1)	31†	30
Km(3)	89†	90

* Values are the percentage of the population. Gm = IgG heavy chain; Km = κ light chain (see Table 1 for other definitions).
 † n = 124.

Table 4. Comparison of Gm and Km allotypes in Mesoamerican IIM patients and healthy Mesoamerican controls*

Gm or Km allotype	Patient subset				Antibody subset		Controls (n = 133)
	All IIM (n = 65)	Adult IIM (n = 51)	Juvenile IIM (n = 14)	Adult DM (n = 34)	Adult anti-Mi-2 (n = 16)	Adult MSA negative (n = 33)	
Gm(1)	98†	98	100	97	100	97	85
Gm(2)	31	29	36	32	44	24	54
Gm(3)	78	75	93	79	88	70	68
Gm(17)	98†	98	100	97	100	97	85
Gm(23)	52	61	21	62	69	61	39
Gm(5)	80	76	93	82	88	73	83
Gm(6)	0	0	0	0	0	0	0
Gm(13)	80	76	93	82	88	73	83
Gm(21)	97†	96	100	97	100	94	81
Km(1)	53‡	52§	54	45‡	25‡	68	81
Km(3)	88‡	91‡	77	94‡	94†	89§	50

* Values are the percentage of the population. Odds ratios (ORs) and 95% confidence intervals (95% CI) for the significant allotypes are as follows: For Gm(1) and Gm(17), OR 11.3 (95% CI 1.6–232); for Gm(21), OR 7.3 (95% CI 1.6–46); for Km(1), all IIM OR 0.3 (95% CI 0.12–0.53), adult IIM OR 0.25 (95% CI 0.11–0.55), adult DM OR 0.19 (95% CI 0.08–0.47), and adult anti-Mi-2 OR 0.08 (95% CI 0.02–0.29); and for Km(3) all IIM OR 7.3 (95% CI 2.9–19), adult IIM OR 10.3 (95% CI 3.3–36), adult DM OR 14.3 (95% CI 3.1–90.3), adult anti-Mi-2 OR 14.8 (95% CI 2–308), and adult MSA negative OR 8 (95% CI 2.2–36). See Tables 1 and 3 for other definitions.

† $P < 0.01$ versus controls.

‡ $P < 0.0001$ versus controls.

§ $P < 0.001$ versus controls.

highest frequency of DM and its associated anti-Mi-2 autoantibody compared with all IIM populations studied to date (Table 6). Of interest, this IIM population is also located closest to the equator and is therefore exposed to the highest levels of natural ultraviolet radiation than any other IIM population ever studied. Conversely, the lowest proportions of DM and of anti-Mi-2 autoanti-

bodies have been seen in an IIM population in Warsaw, Poland, the most northern of the cities similarly studied. These findings are consistent with previous descriptions of latitudinal gradients in the relative prevalence of DM and anti-Mi-2 autoantibodies (32,33). Furthermore, we report another example of genetic risk and protective factors for IIM differing in 2 ethnogeographic popula-

Table 5. Comparison of Gm and Km phenotypes in Mesoamerican IIM patients and healthy Mesoamerican controls*

Gm or Km phenotype	Patient subset				Antibody subset		Controls (n = 133)
	All IIM (n = 65)	Adult IIM (n = 51)	Juvenile IIM (n = 14)	Adult DM (n = 34)	Adult anti-Mi-2 (n = 16)	Adult MSA negative (n = 35)	
Gm 3 23 5,13	2	2	0	3	0	3	14
Gm 1,3,17 5,13,21	28†	22	50‡	24	25	18	10
Gm 1,17 23 21	9‡	10‡	7	3	13	9	0
Gm 1,17 21	8	10	0	9	0	12	9
Gm 1,2,3,17 5,13,21	12	8	29	6	6	9	21
Gm 1,17 23 5,13,21	2	2	0	3	0	3	1
Gm 1,3,17 23 5,13	2	2	7	0	0	3	4
Gm 1,3,17 23 5,13,21	20	24	7	26	19	27	11
Gm 1,2,3,17 23 5,13,21	15	18	0	21	38†	9	8
Gm 1,2,17 23 21	3	4	0	6	0	6	0
Km 1,1	12§	9§	23	6§	6†	11‡	48
Km 1,3	41	43	46	39	19	57	33
Km 3,3	47§	49§	31	55§	75§	32	17

* Values are the percentage of the population. Odds ratios (ORs) and 95% confidence intervals (95% CI) for the significant phenotypes are as follows: for Gm 1,3,17 5,13,21, all IIM OR 3.5 (95% CI 1.5–8.4) and juvenile IIM OR 9.2 (95% CI 2.4–35.8); for Gm 1,17 23 21, all IIM OR 29.2 (95% CI 1.6–526) and adult IIM OR 31.6 (95% CI 1.7–583); for Gm 1,2,3,17 23 5,13,21, adult anti-Mi-2 OR 9.2 (95% CI 2.4–35.8); for Km 1,1, all IIM OR 0.15 (95% CI 0.06–0.36), adult IIM OR 0.10 (95% CI 0.03–0.32), adult DM OR 0.07 (95% CI 0.03–0.34), adult anti-Mi-2 OR 0.07 (95% CI 0.00–0.54), and adult MSA negative OR 0.13 (95% CI 0.03–0.48); and for Km 3,3, all IIM OR 4.3 (95% CI 2.1–9.0), adult IIM OR 4.4 (95% CI 2.0–9.8), adult DM OR 5.8 (95% CI 2.3–14.6), and adult anti-Mi-2 OR 14.4 (95% CI 3.8–58.7). See Tables 1 and 3 for other definitions.

† $P < 0.01$ versus controls.

‡ $P < 0.001$ versus controls.

§ $P < 0.0001$ versus controls.

Table 6. Comparison of 5 ethnogeographic myositis populations*

	Mesoamerican IIM (this study)	Korean IIM (ref. 25)	Japanese IIM (ref. 34)	Polish IIM (ref. 35)	US Caucasian IIM (ref. 13)
Clinical group	(n = 98)	(n = 50)	(n = 84)	(n = 63)	(n = 146)
PM	27	34	26	18	21
DM	69	40†	52‡	24§	42§
IBM	0	0	0	0	16
CTM	4	24¶	19†	37§	13‡
CAM	0	2	2	0	8
Serologic group					
MSA	(n = 87)	(n = 50)	–	(n = 84)	(n = 186)
Antisynthetase	5	18‡	–	13	16¶
Anti-Mi-2	30	8‡	–	5¶	4§
Anti-SRP	1	6	–	1	1
MAA	(n = 85)	(n = 50)	–	(n = 84)	(n = 212)
RNP	11	17	–	4	5
Ro	4	22†	–	14	6
La	4	2	–	4	4
PM/Scl	1§	4†	–	24	1
Ku	2	0	–	10	NA
HLA allele					
Risk factors	DQA1*03; DRB1*04, *0701	None	DRB1*0803	DQA1*0501; DRB1*0301	DQA1*0501; DRB1*0301
Protective factors	None	DRB1*14	DQA1*0501	DRB1*0201; DRB1*0501	None
Gm and Km allotype (phenotype)					
Gm risk factors	Gm(1); Gm(17); Gm(21) Gm 1, 3,17 5,13,21 and Gm 1,17 23 21 and Gm 1,2, 3,17 23 5,13,21)	None (none)	–	–	None (none)
Gm protective factors	None (none)	Gm(21) (none)	–	–	None (none)
Km risk factors	Km(3) (Km 3,3)	None (none)	–	–	None (none)
Km protective factors	Km(1) (Km 1,1)	None (none)	–	–	None (none)

* Except where otherwise indicated, values are the percentage of the population. Except for the comparison of PM/Scl for which comparisons were made with the Polish IIM patients, all other comparisons were relative to the Mesoamericans. The significant differences noted are after correction for multiple comparisons. MAA = myositis-associated autoantibodies (see Tables 1 and 3 for other definitions).

† $P < 0.01$.

‡ $P < 0.05$.

§ $P < 0.0001$.

¶ $P < 0.001$.

tions, not only in the specific alleles at the same polymorphic loci (HLA-DRB1 and DQA1), but also in the genetic loci themselves (HLA, Gm, and Km) (25).

While the sampling in ethnicity and geography is limited and may reflect referral or other biases (13,34,35), other differences in the distributions of global IIM clinical and serologic groups are striking, as are the variations in genetic risk and protective factors in published populations around the world (Table 6). Although attempts were made in all these studies to minimize confounding and biases, by evaluating consecutive subjects who met identical criteria and using predefined standardized questionnaires and evaluations, possible variations in clinical or other assessments may have resulted in different ascertainment. For example, although there is epidemiologic and anecdotal evidence

of differences in the frequency of IBM and CAM in different ethnogeographic populations (12,23,36), which suggests that such differences may be due to genetic or environmental heterogeneity among these populations, the paucity of IBM and CAM in Mesoamericans and in other populations compared with the US Caucasian IIM population may also be a result of referral bias or possibly a limitation in the diagnostic capabilities at certain centers. In addition, because patient populations studied at referral centers may not be representative of the total IIM populations from which they are drawn, extrapolation of these referral data to entire IIM patient populations may not be warranted. Overall, however, we do not believe that referral and assessment biases alone could account for the many significant differences seen among these populations.

For reasons that remain unexplained, anti-Ro autoantibodies were seen most frequently in Korean IIM subjects and anti-PM/Scl autoantibodies were most common in Polish patients. Regarding genetic factors, although Caucasian IIM patients from the US and from Poland have similar HLA risk factors (DRB1*0301 and DQA1*0501), HLA-DRB1*0201 and DRB1*0501 are unique protective factors for myositis in Poland (35). In Japanese IIM patients, HLA-DQA1*0501, which is a risk factor for Caucasians, is a protective allele, while HLA-DRB1*0803 may be a unique risk factor for the development of myositis in the Japanese (34).

Surprisingly, myositis patients from Korea and Mesoamerica shared certain similarities as well as similar differences in genetic risk factors compared with Caucasians. Although HLA genes do not appear to be risk factors for the overall myositis cohorts in either the Mesoamerican or Korean populations, HLA associations were seen among subsets of Mesoamerican IIM populations. Conversely, while no Gm or Km allotype was found to be a risk or protective factor in Caucasian IIM patients, many Gm and Km allotypes and phenotypes were identified as risk or protective factors in both Koreans and Mesoamericans. This suggests another interesting parallel between the Korean and Mesoamerican populations, which have been reported to be both paleoanthropologically and phylogenetically related (37).

Although the number of patients studied was relatively small, our investigations also define the first differences in genetic risk factors between adult and pediatric IIM in the same ethnogeographic group, implying potential differences in pathogenesis of myositis based on the age at disease onset, as has been suggested for other autoimmune diseases (38,39). In contrast to Caucasians, among whom juvenile IIM and adult IIM patients appear to share the same genetic risk factors (15), in Mestizos, juvenile and adult myositis patients have different Gm/Km allotype and phenotype risk factors (Tables 4 and 5). Particularly striking was the finding that Gm 1,2,3,17 23 5,13,21 was a unique risk factor for the development of anti-Mi-2 autoantibodies in adults, but was not seen in any of the 8 juvenile anti-Mi-2-positive patients tested.

It is not clear what may account for these many phenotypic and genetic differences in IIM around the world. Among the possibilities are different environmental risk factors, differing pathogenesises, or the role of other, as-yet-unidentified genetic loci which may be responsible for the development of myositis or some of

its clinical or immunologic manifestations in these populations. It is tempting to speculate that different gene-environment interactions may account for these differences, inasmuch as it is highly probable that relevant environmental exposures differ around the world. For example, the interesting differences in Gm/Km factors in Mesoamerica, which are associated with different antibody levels in response to certain infections (40), are consistent with the possible role of infectious agents in the pathogenesis of some IIM populations; this has been hypothesized in case reports, serologic investigations, and molecular studies (41). Further support for this hypothesis comes from the much higher infectious disease burden in Mesoamerica compared with the US and other more industrialized countries (42).

Despite the fact that we made every attempt in our study design to avoid confounding, by careful evaluation of large populations of clinically well-defined, consecutive patients, using identical criteria and standardized questionnaires, and although we do not know of any trivial explanations for the differences seen between Mestizo and Caucasian IIM populations, potential confounders of this and other comparable studies do exist. These include possible referral bias, nonrepresentative populations due to small sample sizes, or differing assessment capabilities and genetic heterogeneity in study and control populations. Nonetheless, we believe that following clues generated by similar studies around the world will likely enhance the deciphering of the pathogenesises of complex diseases. Comprehensive, worldwide phenotypic and multiloci genetic evaluations of IIM and other autoimmune diseases could ultimately improve our capacity to define the pathogenesises of these increasingly recognized disorders.

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