Chapter | Seven

# Gene—Gene and Gene—Environment Interactions in Defining Risk and Spectrum of Phenotypes in Idiopathic Inflammatory Myopathies

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## 7.1 CLINICAL INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of potentially serious conditions defined by the development of an acquired proximal muscle weakness, elevated levels of skeletal muscle-specific enzymes, characteristic neurophysiological abnormalities, and characteristic inflammatory cell infiltrations in diagnostic muscle biopsies. Although glucocorticoids, various immunosuppressive agents, and intravenous immunoglobulins are all potentially effective in treating IIM, the response to these therapies is variable and often disappointing, i.e., IIM can sometimes be refractory to treatment. Patients can occasionally die from their disease, though the



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majority survive to suffer varying degrees of disability through persisting weakness and/or interstitial lung disease-related breathlessness. Given the limited efficacy of the available therapeutic agents in IIM, new and more potent therapies are clearly required, but facilitating their development will require that etiopathological mechanisms are better understood, in order to direct disease-specific drug developments. Given the rarity of IIM, with an annual incidence range of 2.18−7.7 cases per million [1], mechanistic research has proved considerably difficult, so disease pathways remain largely unelucidated.

It is increasingly clear from immunogenetic research that IIM disease susceptibility is closely associated with human leukocyte antigen (HLA) genes, which likely interact with environmental factors in a manner common for complex diseases to trigger disease onset [2]. IIM may be classified by "traditional" clinical subtype, i.e., polymyositis (PM), dermatomyositis (DM), myositis overlapping with another connective tissue disease (CTD), IBM and juvenile DM (JDM). While certain HLA genes are clearly associated with the classical clinical phenotypes, PM, DM, and IBM, it has been suggested that IIM may be better classified serologically, i.e., according to the presence of circulating myositis-specific or myositis-associated antibodies (MSAs/MAAs), the differential presence of which strongly predicts an individual's overall subtype within the IIM disease spectrum [3,4]. Furthermore, which MSA/MAA an individual IIM patient will develop appears predictable from their HLA genotype [5,6]. Given that MSAs/MAAs are gene products predictable from an individual's HLA genotype, and that IIM subtype is predictable from myositis serology, this may suggest that the disease subtype (including myositis serotype) of an individual destined to develop IIM is in fact predetermined by their genotype at HLA, rather than by the nature of any disease-inducing environmental trigger. The latter may instead be responsible for inducing disease through generic intracellular mechanisms somehow relating to HLA genes, or gene−environmental interactions. An unresolved mystery in IIM relates to the detection of a growing number of MSAs, whose antigen targets are not muscle specific but ubiquitous and present in all cells. Moreover, all of these antigen targets are intracellular, and thus normally invisible to the immune system [7], so it remains unclear how skeletal muscles become a target for the immune system.

Recent reviews have discussed the considerable progress made in our understanding of IIM immunogenetics and the potential implications for differential disease expression including circulating MSA/MAA [8,9]. However, how overall IIM phenotypes are mechanistically linked to HLA class I or II genes and environmental triggers, or their interplay, are currently unknown. This chapter reviews recent immunogenetic study results to explore the hypothesis that HLA genes and HLA gene−gene and HLA gene−environment interactions play central roles in determining not only susceptibility, but also disease subtype including treatment outcomes in the IIM disease spectrum.

## 7.2 EARLY HLA RESULTS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

The earliest evidence suggesting that genetic factors are involved in IIM disease susceptibility, and as extensively reviewed by Shamin et al. in 2000 [10], came largely from candidate gene studies, as the rarity of IIM had precluded the use of more robust genetic methods, such as twin studies, whole genome scans or multicase family studies with transmission disequilibrium testing. However, case reports with multiple affected family members [11] clearly suggested a familial predisposition for developing IIM. Given the role that HLA class II genes play in disease susceptibility in other autoimmune diseases such as rheumatoid arthritis (RA), it was obvious that genetic research in IIM would commence in this area. Thus, it was confirmed that HLA-DRB1*03 (DR3) and homozygosity at HLA-DQA1 both represented risk factors for developing familial IIM [12]. Candidate gene studies in nonfamilial IIM have mainly concentrated in the HLA class II region, confirming that HLA-DRB1*0301, and the linked allele HLA-DQA1*0501, do indeed represent risk factors for developing IIM in Caucasians, though not in Mesoamerican Mestizo, Korean, or Japanese populations [13]. However, these early candidate studies were somewhat small and grouped ethnically heterogeneous adult and juvenile PM, DM, and adult IBM patients together in order to maximize statistical power.

## 7.3 HLA-RELATED DIFFERENCES IN PM/DM

Given the obvious clinical and histopathological differences detectable between traditional PM and DM [14], a more logical genetic approach would be to compare and contrast, rather than group, these diseases during case−control comparisons. In order to overcome the sample size issue, a UK-wide collaboration ("UK-Adult Onset Myositis Immunogenetic Collaboration," AOMIC) was commenced in 1999 (relabeled UK-MYONET since 2008). The investigative strategy utilized was to correlate HLA genotype with myositis serotype and overall clinical phenotype. The UK-AOMIC recruited 109 PM and 103 DM UK adult Caucasian patients by 2004. These patients' HLA-DRB1 results were compared with those of 537 ethnically matched controls. The results confirmed HLA-DRB1*03 as a risk factor for PM (odds ratio (OR) 4.0, 95% confidence interval (CI) 2.6−6.1) (Figure 7.1).

However, there was also a significant protective effect of HLA-DRB1*07 in PM versus controls (OR 0.3, 95% CI 0.4−0.6). In contrast, although HLA-DRB1*03 was clearly also a risk factor in DM, the association was considerably weaker than for PM (OR 2.0, 95% CI 1.3−3.1) and moreover, DRB1*07 represented a significant risk factor in DM versus controls (OR 1.8, 95% CI 1.2−2.9). The results of this study, which were the first to demonstrate a significant genetic difference between PM and DM in UK Caucasian cases, suggested that, at least in this population, HLA-DRB1 governs not only PM/DM disease susceptibility, through association with

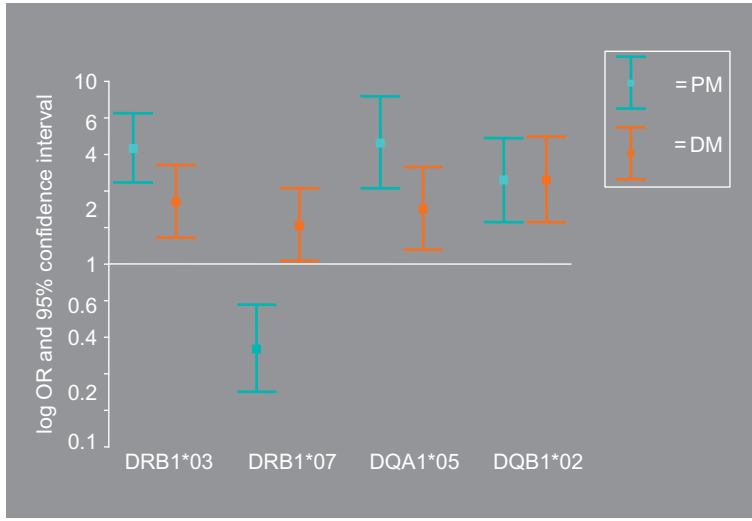


**FIGURE 7.1** HLA class II associations in polymyositis and DM. OR, odds ratio; PM, polymyositis; DM, dermatomyositis.

DRB1*03, but also IIM phenotype, i.e., likelihood of PM versus DM, through differential associations with DRB1*07 [5]. The results of early research in Japanese IIM cohorts demonstrated obvious genetic association differences compared with those from US and UK Caucasian IIM cases, and where HLA-DQA1*0501 represented a protective rather than a risk factor in Japanese cases and where small but significant differences between PM:DM HLA were apparent, as summarized by Shamin et al. [10]. As well as emphasizing the importance of ethnicity when considering genetic issues in IIM susceptibility, these combined results clearly suggest that gene—gene interactions at HLA class I and II (and especially around DR) genes may play an important role in defining IIM subtype, or represent a marker for other contributory factors, e.g., other alleles in linkage disequilibrium (LD) with DRB1 but forming part of larger haplotypes.

## 7.4 THE ASSOCIATION BETWEEN HLA GENES, CLASS II HAPLOTYPES, AND MSAS/MAAS

As collaborative IIM cohorts have grown and autoantibody detection has improved, so that more and more MSA/MAA subtypes have been detected in larger IIM subtype cohorts, it has become clear that IIM "phenotyping by serosubtype" does indeed give more homogeneous cohorts, as was previously predicted [3,4]. For instance, the anti-Jo-1 antibody (Ab) is associated with myositis in combination with Raynaud's phenomenon, arthritis, interstitial lung disease, and so-called mechanics' hands, otherwise known as the antisynthetase syndrome [15,16], irrespective of whether the patient has traditional PM or DM, and the anti-SRP Ab is associated with an aggressive,

treatment-resistant necrotizing myopathy and usually in the absence of a DM-specific rash [17,18]. In contrast, the anti-Mi-2 Ab is DM-specific and associated with hallmark DM rashes with muscle inflammation which is predictably treatment-responsive [3,19]. An early study investigating the association between HLA genes and MSA status interrogated at HLA-DRB1, -DQA1, and -DQB1 in 224 patients with IIM [20]. The results in Caucasians showed significant associations of MSA (and mostly anti-synthetase Ab) with the HLA-DRB1*0301, -DQA1*0501, and -DQB1*0201 alleles (and haplotype) in PM, DM, and IIM overall. In African-Americans, however, only HLA-DQA1*0501 was significantly increased, and then not in DM cases, while in Mexican-Americans and Japanese patients, this allele was not increased in any subtype. When the authors analyzed all ethnic groups together, only HLA-DQA1*0501 was still significantly increased and again not in DM patients. It was concluded that genetic susceptibility for anti-Jo-1 and other MSA was mainly localized within the major histocompatability complex (MHC) region at HLA-DQA1*0501, although this allele was not associated with the presence of anti-Mi-2 Abs. A potential criticism of this study was that, although the overall patient cohort was reasonably large, analytical stratifications by ethnicity, disease subtype, or MSA considerably reduced the available statistical power. Given that anti-Mi-2 Abs were already considered DM specific around this time [3] and that the Arnett et al. study [20] had shown no HLA association with anti-Mi-2 Abs, other investigators undertook immunogenetic studies specifically targeting anti-Mi-2 positive patients [21]. The results showed strong associations between the presence of anti-Mi-2 and the HLA DRB1*0701 and DQA1*0201 alleles, an association which was even stronger in those patients homozygous for HLA-DRB1*0701, though no statistically relevant HLA-DQB1 associations were found [21]. These early studies clearly suggested a strong association between individual HLA genes, and possible haplotypes, with myositis serotypes, as reviewed by Shamin et al. [10].

In our early AOMIC studies, we studied relatively larger groups of Caucasian only patients, so we did have relatively more statistical power than that of the earlier studies cited. In our studies, we genotyped HLA-DRB1 and HLA-DQA1 alleles, and so were able to derive alleles at HLA-DQB1 [5]. Thus, we were able to show for the first time that DQB1*02 represents a similarly sized risk factor for PM and DM. We were also able to clearly elucidate HLA class II haplotypes at DRB1-DQA1-DQB1. In a haplotype, due to genetic structure of the locus with high LD and rare recombinations, the genetic variants are inherited in a block together through successive generations more often than would be expected by chance [22]. As we had also comprehensively serotyped MSA/MAA by immunoprecipitation in the same cohorts, we were able to confirm that an individual's Ab status is closely associated with their HLA class II haplotype (Table 7.1), as well as with the individual HLA class II alleles already discussed (for up-to-date summary of associations of individual HLA class I and II alleles with IIM, see Table 7.2).

**TABLE 7.1** Estimated HLA DRB1-DQA1-DQB1 Haplotype Frequencies in IIM

| DRB1-DQA1-DQB1 haplotype | % Controls $2n = 284$ | PM Overall $2n = 220$ | DM Overall $2n = 208$ | Other Abs[a] AS $2n = 98$ | Mi-2 $2n = 36$ | PM-Scl $2n = 22$ | U1-RNP $2n = 24$ | SRP $2n = 12$ |
|---|---|---|---|---|---|---|---|---|
| 04-03-03 | 20.4 | 16.4 | 19.1 | 17.3 | 13.8 | 4.5 | 37.5 | 0 |
| **03-05-02**[b] | **16.5** | **33.6** | **24.5** | **43.9** | **8.3** | **54.5** | **12.5** | **4.1** |
| 02-01-06 | 13.7 | 9.1 | 9.6 | 10.2 | 8.3 | 4.5 | 20.8 | 25.0 |
| 01-01-05 | 10.6 | 11.8 | 13.5 | 7.1 | 22.2 | 9.1 | 16.7 | 8.3 |
| 13-01-06 | 10.2 | 6.4 | 5.8 | 6.1 | 0 | 4.5 | 1.0 | 8.3 |
| **07-02-02**[c] | **9.2** | **4.1** | **13.9** | **7.1** | **33.3** | **18.2** | **0** | **0** |
| 11-05-03 | 4.6 | 7.3 | 5.3 | 2.0 | 5.6 | 0 | 0 | 16.7 |
| 07-02-03 | 3.9 | 0.4 | 3.8 | 0 | 5.6 | 0 | 1.0 | 0 |

[a] *PM and DM patients combined.*
[b] *PM versus controls,* $P = 1.1 \times 10-4$, *OR 2.6 (1.6–4.0); AS versus controls,* $P = 7 \times 10^{-10}$, *OR 4.8 (2.8–8.3); PM-Scl versus controls,* $P = 0.001$, *OR 6.1 (2.2–16.5).*
[c] *PM versus DM,* $P = 0.004$, *OR 0.3 (0.1–0.6); Mi-2 versus controls,* $P = 0.002$, *OR 4.9 (2.0–11.6).*
*Probabilities stated are corrected for multiple comparisons; haplotypes found in less than 3% of controls are excluded from the table. PM, polymyositis; DM, dermatomyositis; AS, anti-tRNA synthetase positive.*

**TABLE 7.2** Individual HLA Class I and II Gene Associations in IIM Serological Groups, by Ethnicity

| Antibody | Ethnicity | HLA allele | *P* value | OR, 95% CI | Reference |
|---|---|---|---|---|---|
| **Anti-Jo-1** | Caucasian | DRB1*0301 | $P = 0.00004$ | 9.6, 2.9–36.3 | [20] |
| | | | $p_{corr} < 0.0001$ | 15.5, 8.3–30.2 | [6] |
| | | DQB1*0201 | $p = 0.0002$ | 8.3, 2.2–46.1 | [20] |
| | | | $p_{corr} < 0.0001$ | 21.7, 9.4–55.4 | [6] |
| | | B*08 | $p_{corr} < 0.0001$ | 15.7, 6.4–41.5 | |
| | | C*0701 | $p_{corr} = 0.008$ | 0.3, 0.1–0.6 | |
| | | *DRB1*01* | $p_{corr} < 0.0001$ | 0.1, 0.1–0.4 | |
| | | *DQA1*0201* | $p_{corr} < 0.0001$ | 5.1, 2.7–10.4 | |
| | | DQA1*0501 DPB1*0101 | $p_{corr} < 0.00003$ | 4.1, 2.1–7.8 | [23] |
| **Anti-Jo-1** | African-American | B*08 | $p = 0.02$ | 7.6, 2.1–27.4 | [24] |
| | | DRB1*0301 | $p = 0.001$ | 6.7, 2.5–18.0 | |
| **Anti-PL-7** | Caucasian | C*0304 | $p_{corr} = 0.05$ | 25.3, 2.2–1257.8 | [6] |
| **Anti-PL-12** | Caucasian | DRB1*0301 | $p_{corr} = 0.01$ | 13.5, 2.6–131.2 | [6] |
| **Anti-synthetase** | Caucasian | DRB1*03 | $p_{corr} = 1 \times 10^{-14}$ | 14.1, 6.3–35.2 | [5] |
| | | DRB1*0301 | $p_{corr} < 0.008$ | 40.1, 4.2–1861 | [25] |
| | | DQA1*05 | $p_{corr} = 4 \times 10^{-08}$ | 9.5, 3.8–36.5 | [5] |
| | | DQA1*0501 | $p_{corr} < 0.008$ | 16.7, 1.9–770.2 | [25] |
| | | DQB1*02 | $p_{corr} = 4 \times 10^{-08}$ | 9.5, 3.8–36.5 | [5] |
| **Anti-Mi-2** | Caucasian | DRB1*07 | $p_{corr} = 0.00005$ | 11.1, 3.4–46.8 | [5] |
| | | DRB1*0701 | $p < 0.0001$ | 22, 4.6–105 | [21] |
| | | | $p < 0.001$ | 18.7, 2.1–873.4 | [13] |
| | | | $p_{corr} = 0.002$ | 4.9, 2.2–11.5 | [6] |
| | | DQA1*02 | $p_{corr} = 0.00005$ | 11.6, 3.3–50.6 | [5] |
| | | DQA1*0201 | $p < 0.0001$ | 20.2, 4.4–93 | [21] |
| | | | $p < 0.001$ | 19.8, 2.2–923.3 | [13] |
| | | | $p_{corr} = 0.002$ | 3.3, 1.5–7.5 | [6] |
| | | DQB1*02 | $p_{corr} = 0.004$ | 7.5, 2.0–41.9 | [5] |
| **Anti-Mi-2** | Hispanic | DRB1*04 | $p_{corr} < 0.01$ | 4.7, 1.7–13.3 | [13] |
| | | DQA1*03 | $p_{corr} < 0.001$ | 7.0, 2.3–22.8 | |
| **Anti-Mi-2** | African-American | DRB1*0302 | $p = 0.0005$ | 23.6, 4.2–234.2 | [6] |
| | | DQA1*0401 | $p = 0.0008$ | 25.2, 3.2–1106 | |
| **Anti-SRP** | Caucasian | B*5001 | $p_{corr} = 0.02$ | | [6] |
| **Anti-SRP** | African-American | DQA1*0101 | $p = 0.04$ | 3.6, 1.4–9.8 | [24] |
| **Anti-PM-Scl** | Caucasian | DRB1*03 | $p < 0.0001$ | | [26] |
| | | | $p < 0.0001$ | 10.6, 3.4–38.7 | [27] |
| | | | $p_{corr} = 0.00004$ | 30.6, 4.4–1309.1 | [5] |
| | | DRB1*0301 | $p_{corr} < 0.008$ | 100, 13.1–4258 | [25] |
| | | | $p_{corr} < 0.0001$ | 77.5, 19.6–663.8 | [6] |

*(Continued)*

**TABLE 7.2** (continued)

| Antibody | Ethnicity | HLA allele | *P* value | OR, 95% CI | Reference |
|---|---|---|---|---|---|
| | | *DQA1*0101* | $p_{corr} = 0.003$ | 0.2, 0.05—0.5 | [6] |
| | | DQA1*05 | $p_{corr} = 0.001$ | 18.9, 2.6—814.9 | [5] |
| | | DQA1*0501 | $p_{corr} < 0.008$ | 16.5, 1.9—763.4 | [25] |
| | | | $p_{corr} < 0.0001$ | 15.2, 4.8—77.1 | [6] |
| | | DQB1*02 | $p_{corr} = 0.001$ | 18.0, 2.5—777.4 | [5] |
| **Anti-Ku** | Caucasian | DRB1*0301 | $p_{corr} < 0.008$ | 38.1, 4.1—1768 | [25] |
| | | DQA1*0501 | $p_{corr} < 0.008$ | 16.5, 1.9—763.4 | [6] |
| | | DRB1*11 | $p_{corr} < 0.04$ | 21.3, 2.1—1049.8 | |

*Key:* p *values are uncorrected (unless otherwise stated), associations given are odds ratios and 95% confidence intervals versus controls,* $p_{corr}$ *= corrected* p *value. Alleles in italics refer to protective factors.*
**Source**: *Adapted from Ref. [9].*

It was also apparent that HLA class II haplotype associates more strongly with Ab status than with traditional overall PM or DM phenotype. Despite our relatively large AOMIC cohorts, and because many of the MSAs/MAAs and their associated phenotypes are so rare, we could only demonstrate statistically significant associations between the HLA class II DRB1*03-DQA1*05-DQB1*02 haplotype and possession of anti-Jo-1 Abs, irrespective of whether the case was traditional PM or DM in type, and between the HLA class II DRB1*07-DQA1*02-DQB1*02 haplotype and possession of anti-Mi-2 Abs, but specifically in the traditional hallmark DM subtype. Our early AOMIC cohort results did also show increases (versus controls) in the HLA class II DRB1*02-DQA1*01-DQB1*06 haplotype in anti-SRP Ab positive cases and increases in the HLA class II DRB1*04-DQA1*03-DQB1-03 haplotype in UI-RNP Ab positive cases, but the numbers of cases with these Abs were too small to show that these haplotype—Ab associations were significant [5]. It may in future be possible with much larger collaborative subtype cohorts collected through international collaborations to demonstrate that all MSAs/MAAs are significantly associated with specific HLA genes and/or haplotypes. It has recently been established by another research group that there is a statistically significant association between possession of the anti-200/100 Ab and HLA-DRB1*11:01 in Caucasian patients suffering with statin-induced myopathy [28], to be discussed later. Given that MSAs/MAAs are gene products apparently predictable by an individual's HLA genotype, this may with further research eventually mean that IIM would be more logically classified according to HLA genotype, and for which the relevant MSA/MAA would then represent a surrogate marker. An up-to-date summary of the currently detectable MSA, their intracellular antigen targets, and their IIM subtype associations are given in Table 7.3 [7].

Although there are rare case reports of IIM patients possessing more than one anti-synthetase Ab [29], it is generally accepted that MSAs are mutually

**TABLE 7.3** Currently Detectable MSAs, and Their Target Autoantigens and Clinical Associations

| Autoantibody | Target Autoantigen | Clinical Associations | Frequency | |
|---|---|---|---|---|
| | | | Adults (%) | JDM (%) |
| Anti-ARS | Aminoacyl-tRNA synthetase | Anti-synthetase syndrome | Overall: 30–40 | Overall: 1–3 |
| Jo-1 | Histidyl | Myositis | Jo-1: 15–20 | |
| PL7 | Theronyl | ILD | PL7: <5 | |
| PL12 | Alanyl | Raynaud's phenomenon | PL12: <5 | |
| OJ | Isoleucyl | Arthritis | OJ: <5 | |
| EJ | Glycyl | Mechanic's hands | EJ: <5 | |
| KS | Asparaginyl | Fever | KS: <5 | |
| Ha | Tyrosyl | | Ha: <1 | |
| Zo | Phenylalanyl | | Zo: <1 | |
| Anti-Mi-2 | Nucleosome remodeling deacetylase complex (NuRD) | DM | <10 | <1 |
| Anti-p155/140 | Transcriptional intermediary factor 1 Gamma/alpha (TIF1 gamma/alpha) | JDM: DM and ulceration Adults: DM and malignancy | 13–21 | 23 |
| Anti-p140 | Nuclear matrix protein 2 (NXP2) | JDM: DM and calcinosis Adults: DM and malignancy | < 5 | 18–29 |
| Anti-SAE | Small ubiquitin-like modifier activating enzyme (SAE) | DM | <5 | <1 |
| Anti-CADM140 | Melanoma differentiation Associated gene 5 (MDA5) | JDM: DM and ILD Adults: CADM and ILD | < 5 (50–70 in CADM) | 7–38 |
| Anti-SRP | Signal recognition particle (SRP) | Necrotizing myopathy | 5–10 | <1 |
| Anti-HMG-CoA | 3-Hydroxy-3-methylglutaryl-CoA reductase | Statin-induced necrotizing myopathy | <10 necrotizing myopathy | Not known |

**Source**: *Adapted from Ref. [7].*

exclusive, although patients can coincidentally also possess one or more MAA. It was therefore of great interest to discover that, in those AOMIC patients homozygous for HLA-DQB1*02 (and thus be able to posses *both* the HLA DRB1*03-DQA1*05-DQB1*02 and DRB1*07-DQA1*02-DQB1*02 class II haplotypes) if an Ab was detected then this was *always* an anti-Jo-1 rather than an anti-Mi-2 in type [5]. This is clear evidence that one class II haplotype can dominate or "trump" another with regard to associated Ab

production, and that class II haplotypes are likely more important than individual HLA genes within those haplotypes with regard to determining Ab production, and overall phenotype. Given the clinical and prognostic implications of possessing anti-Jo-1 Abs, such as the potential for lethal right heart failure secondary to ILD in PM and DM, versus those of possessing anti-Mi-2 Abs, where there is a likely good treatment response and little or no ILD risk, this clearly shows that interactions within and between these HLA class II genes within or between haplotypes govern not only disease susceptibility, but also treatment responses and outcomes through the differential subtypes which result from those genetic interactions.

While accepting the notion that HLA class II haplotype is an important parameter governing overall IIM phenotype, including serotype, the early AOMIC work has also shown that the interrelationship between HLA class II genes and haplotypes is complex. Given that MSAs are so mutually exclusive and given the strength of association between HLA genotype, myositis serotype, and overall IIM phenotype, it was thus a considerable surprise to discover that the HLA class II DRB1*03-DQB1*05-DQB1*02 haplotype is significantly associated with possession of either anti-Jo-1 or anti-PM-Scl Abs, but not both [5,23]. It is accepted that patients with these Abs represent separate phenotypes with differing clinical features and outcomes [3,26], but the phenotypes associated with these Abs have distinct similarities. Thus, both suffer with Raynaud's phenomenon, myositis, and ILD, though those with anti-PM-Scl Abs also develop a variable degree of sclerodermatous features which are noted as very unusual in our own anti-Jo-1 positive adult PM cases. Moreover, while nearly all JDM cases initially present with classic dermal DM features, a proportion of cases then lose these classic features over time, to evolve sclerodermatous skin features in association with possession of anti-PM-Scl Abs (i.e., "scleromyositis") [30], thus emphasizing the clinical importance of knowing an individual patient's MSA/MAA status. These subtle clinical phenotype differences prompted us to specifically probe these two IIM subsets (in adult and juvenile cases) at other HLA class II genes to try to account for these Ab−phenotype association differences. We thus compared these patient subgroups at HLA-DPB1. Relative to the discussed HLA DRB1-DQA1-DQB1 genes, the DPB1 gene resides on the other side of at least one recombination "hot spot" [31]. Such a separation weakens the degree of LD between HLA-DPB1 and these other class II genes. The DPB1 results showed that this gene could discriminate between the DRB1*03/anti-Jo-1 positive cohort, which was statistically also associated with DPB1*0101 (versus controls, OR 4.1, CI 2.1−7.8, $P = 3.0 \times 10^{-5}$) and the DRB1*03/anti-PM-Scl positive cohort, which was not associated with DPB1*0101 (versus controls, OR 1.2 CI 0.36−3.3, $P =$ not significant) [23] (Figure 7.2).

These results represent clear evidence that multiple HLA class II gene−gene interactions are involved in governing the overall IIM clinical phenotype, including serological subtype, and may again help explain why

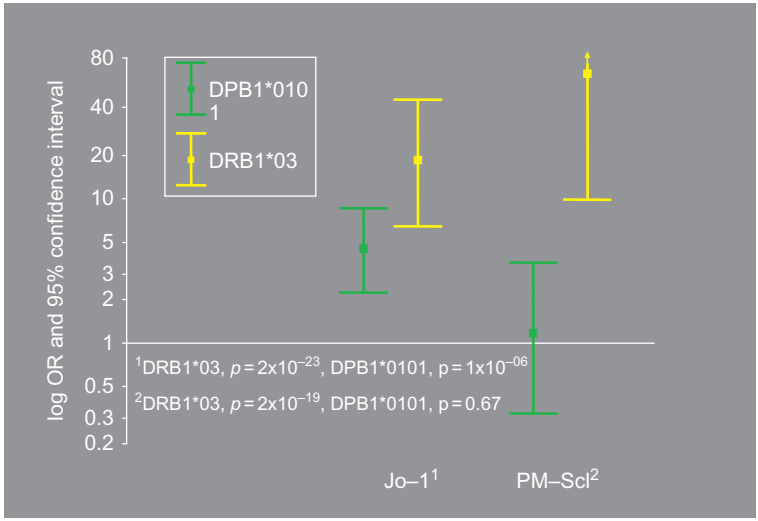


**FIGURE 7.2** HLA-DPB1*0101 and DRB1*03 associations in Jo-1 and PM-Scl Ab positive cases versus controls. OR, odds ratio.

MSAs are so mutually exclusive. These results thus suggest that extended haplotypes at least containing DRB1-DQA1-DQB 1-DPB1 genes are important in defining subtypes within the IIM disease spectrum.

It is interesting to note that, in the only genome-wide association scan (GWAS) done to date in Caucasian IIM cases (in 1178 DM/JDM cases versus 4724 controls), no statistically significant genome-wide associations have been found for any SNP outside of the MHC [32]. This contrasts dramatically with GWAS results from RA, SLE, T1D, and other autoimmune diseases, where a very large number of statistically significant susceptibility loci have been confirmed in studies with much greater statistical power than has been possible to date in IIM, but where the translational or functional significance of these identified susceptibility loci is yet to be elucidated [33].

## 7.5 CONTRIBUTION OF HLA-DRB1 GENE DOSE TO DISEASE PHENOTYPE AND SEVERITY IN IBM

In previous reviews, sporadic IBM is described as the commonest acquired muscle disease in older people. Although muscle biopsies do show inflammatory cell infiltrates very similar to those of PM, IBM is notoriously nonresponsive to glucocorticoids and/or other immunosuppressive agents [34]. A characteristic IBM patient will present with simultaneous weakness and muscle atrophy of the quadriceps femoris and forearm finger flexor muscles, but the latter muscles are not always weak at disease onset, so patients are often initially misdiagnosed as PM. The correct IBM diagnosis may then

become only gradually clear over time in an apparently treatment refractory PM case, i.e., when forearm finger flexor muscle weakness has eventually evolved and by when (usually multiple repeat) muscle biopsies eventually demonstrate histopathological features typical of IBM, including rimmed vacuoles and inclusions [34,35]. The genetics of IBM have been investigated in relatively small patient numbers, though the results do clearly confirm that HLA DRB1*0301 is significantly involved in conferring IBM susceptibility [36,37]. However, it has also been shown that gene−gene interactions at DRB1 not only influence IBM disease susceptibility but also clinical phenotype. Thus, patients possessing both the HLA DRB1*0301 and the DRB1*0101 alleles develop their disease nearly a decade earlier and weaken more rapidly than patients who are DRB1*0301 positive but DRB1*0101 negative. Thus, having a "double dose" of DRB1 susceptibility genes is associated with more severe IBM disease [36,37]. As IBM is a progressive disease with a potential for lethal outcome, these gene−gene interactions have got obvious clinical implications. Similar interaction between two HLA genes to increase disease susceptibility has been clearly demonstrated in other rheumatic disease such as ankylosing spondylitis, where patients possessing the HLA class I genes B27 and B60 have a dramatically increased relative risk compared with those patients possessing only B27 or B60 [38]. The relation between HLA genotype and MSA/MAA is unclear in IBM, due to the small size of all of the genetic studies done to date and since no correlation between HLA genes with MSA/MAA by the gold standard of immunoprecipitation has yet been undertaken here. Given the strength of the association between HLA genes and myositis serology in IIM, undertaking such a correlation in larger cohorts of IBM patients for comparison with well-defined PM cases would now appear vital, as this could help to definitively determine whether or not PM and IBM share the same genetic susceptibility. If DRB1*03 positive IBM patients do not produce anti-Jo-1 or anti-PM-Scl Abs, this would clearly suggest differential disease mechanisms between PM and IBM. As for IIM, the initiating trigger/s for IBM-induction is/are unknown.

## 7.6 REMARKABLE LESSONS FROM STATIN-INDUCED MYOSITIS

Recently a new IIM subset has been described in association with an HLA-DR genotype, a so-called necrotizing myopathy that is associated with Abs against anti-3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This anti-HMG-CoA reductase Ab positive necrotizing myopathy is highly associated with HLA-DRB1*1101 (OR 10.4, 95% CI 3.6−31.4, $P = 1.2 \times 10^{-6}$, [28]) and is strongly associated with previous use of statins, which work by selectively inhibiting HMG-CoA reductase. Therefore, it appears that statins can induce an immune response with autoantibodies directed toward HMG-CoA reductase in individuals with a certain HLA type.

However, where the initial immune reaction takes place is unclear as this myopathy is characterized histopathologically by muscle fiber necrosis accompanied by infiltration with macrophages, rather than the usual T or B cell infiltrates seen in PM/DM in muscle tissues. Furthermore, it is not known whether these HMG-CoA reductase Abs are a primary immune process event present before the clinical manifestations of this myopathy, or whether they may be secondary and only appear following the resulting muscle fiber damage [39–41]. As HMG-CoA resides in the endoplasmic reticulum (ER) membrane [42], it was hypothesized that treatment-induced dysfunction of this enzyme could cause ER disruption in susceptible individuals [41].

Statins are metabolized by cytochrome P450 in liver [43], so it is interesting to speculate that it may only be homozygous slow (or fast) oxidizers who are also HLA-DRB1*1101 positive who are at risk. Moreover, HMG-CoA reductase will also be under polymorphic genetic control, so it may be that genetically determined fast or slow metabolic status at this locus is also required, over and above the HLA and P450 gene issues outlined, for an individual to develop statin-induced myopathy. The requirement for all these genetic factors, and perhaps others, to simultaneously apply would potentially explain the obvious rareness of statin-induced myopathy, relative to the huge numbers of patients regularly ingesting these drugs without problems. There is increasing evidence that, once initiated, statin-induced necrotizing myopathy does not always settle with drug withdrawal, but instead becomes self-sustaining and so may require immunotherapeutic interventions [42].

## 7.7 CANCER-ASSOCIATED MYOSITIS (CAM), HLA, AND ANTI-155/140 AUTOANTIBODIES

An exciting recent IIM development has been the discovery of the anti-155/140 Ab [44–48]. The antigen target for the 155-kd portion of this Ab is human transcriptional intermediary factor γ (TIF1γ), also known as TRIM33, Ret-fused gene 7, PTC 7, or ectodermin, a nuclear member of the TIF1 gene family. This Ab is DM-specific and found in up to nearly 80% of adult DM patients with CAM, where this is defined as DM occurring within 3 years either side of an incident cancer [49]. This Ab is not however specific for CAM as it is found in DM patients without cancers. Moreover, many cancer types are associated with this Ab, i.e., there does not appear to be any link with specific cancers. The antigen target of the 140-kd portion of the Ab is TIF-1α. TIF-1β (100 kd) is also targeted in DM patients but less frequently than TIF-1α and TIF1γ [47]. CAM is thought to represent a paraneoplastic reaction to incident cancers, and the strategic importance of the 155/140 Ab is that it clearly alerts to the likelihood of a cancer and so directs the need for and intensity of cancer screening [48,50,51]. The anti-155/140 Ab is also found in JDM, indeed it is one of the commonest MSA found in JDM cases, although here it is not associated with cancers but instead associated with more severe skin ulceration [52]. Given the spatial conformity issues

dictating antigen specificity, it is difficult to envisage how various different cancer cell lines can all induce an identical immunological reaction to result in the production of the same anti-155/140 Ab, unless the mechanism is through some generic process common to all the cancers. Given that the cancer cells inducing the myositis are all outside the diseased muscle cells, this suggests some common environmental interaction and possibly with HLA genes. While it seems likely, given the strength of the discussed association between MSA/MAA and HLA class I and II genes and class II haplotypes, that all anti-155/140 Ab positive patients will be of similar HLA genotype, we have to date found no good evidence for such an association, though we have interrogated at HLA-DRB, HLA-DQA, and HLA-DQB in only 16 individuals thus far [51]. A putative association of anti-155/140 has been described with HLA-DQA1*0301 (OR 5.4, 95% CI 2.3−12.5, $p_{corr} = 0.004$) [45]. Further HLA and MHC genetic analyses are clearly required in larger groups of patients possessing this important Ab, and this could be achieved through large international collaborations.

## 7.8 RELATIONSHIP BETWEEN SMOKING, HLA-DRB1*03, AND ANTI-JO-1 IN IIM

It has been shown in RA that smoking interacts with the shared epitope alleles to increase disease susceptibility, but only in patients seropositive for rheumatoid factors and anti-citrullinated protein antibodies (ACPAs) [53−55]. These results were thought to represent clear evidence of an interaction between an environmental factor (smoking) and genetic susceptibility (the shared epitope alleles), with smoking-induced loss of tolerance to citrullinated proteins, and thus susceptibility changes. These RA results prompted a European IIM collaboration to be undertaken to ascertain whether a similar situation applies in IIM. Thus, DRB1*03 status and anti-Jo-1 status (the commonest MSA in adults) were studied in 557 Caucasian IIM nonsmokers and ever-smokers. The results clearly suggested that smoking is associated with an increased risk of possession of anti-Jo-1 in DRB1*03 positive cases, and it was thus hypothesized that an interaction between smoking and HLA-DRB1*03 may prime the development of anti-Jo-1 Abs, i.e., analogous to the interaction between the shared epitope alleles, ACPAs, and smoking in RA [56].

## 7.9 POSSIBLE PATHOGENIC ROLE OF HLA AND AUTOANTIBODIES

HLA may have several roles in the pathogenesis of IIM. The strong association between HLA-DR genotype and specific autoantibodies and the association with distinct clinical phenotypes of IIMs as described above, e.g., for the antisynthetase syndrome, is compelling and could suggest a pathogenic role of HLA in the context of immune reactivity, although the specific antigens involved still need to be determined. This hypothesis is supported by reports

that anti-Jo-1 Abs may precede the onset of myositis clinical manifestations [57], and the many cases described where an anti-synthetase Ab is present in the absence of any evidence of active myositis (e.g., [58–60]). Given the potential interaction between HLA-DR genes and smoking in IIM, it is unclear where the immune reaction starts, as this may be at different sites in different subsets of IIMs, such as skin or lung as these organs are often involved early in the disease process, and sometimes before the onset of myositis. Notably, although the MSAs are myositis specific, they are directed against ubiquitous autoantigens and to date no muscle-specific autoantigens have been identified. The effects of smoking in the context of IIM may be to modify autoantigens in the epithelial cells, e.g., the histidyl-tRNA synthetase, of the lungs and thus give rise to an immune response with anti-Jo-1 autoantibodies being generated in the lungs. A "second hit" may be needed to initiate an immune response directed against the muscles, e.g., trauma and repair of muscle cells, as regenerating muscle fibers have a higher expression of the histidyl-tRNA, the target of anti-Jo-1 Abs, then differentiated muscle fibers. Thus an environmental factor such as smoking may lower the threshold for environmental triggers in a way similarly proposed for RA [53–55]. Further research is clearly required in this important area.

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