Supplementary Table 1. Breakdown of cohort by country of origin and clinical diagnosis.

Origin	DM	IBM	JDM	JPM	PM	Necrotizing	ASS[1]	Total
Australia	19	44	0	0	56	7	0	**126**
Belgium	2	6	0	0	4	15	0	**27**
Czech Republic	119	2	10	0	102	6	0	**239**
Denmark	0	0	46	7	0	0	0	**53**
France	10	19	0	0	6	10	1	**46**
Hungary	60	2	18	1	127	2	0	**210**
Italy	15	2	0	0	15	0	4	**36**
Netherlands	13	9	0	0	16	0	0	**38**
Norway	32	1	5	0	25	0	0	**63**
Switzerland	1	0	0	0	2	0	0	**3**
Sweden	89	31	5	0	143	0	0	**268**
Spain	37	8	1	0	25	0	0	**71**
United Kingdom	289	128	193	4	367	8	6	**995**
United States	146	0	230	0	31	0	0	**407**
Total	**832**	**252**	**508**	**12**	**919**	**48**	**11**	**2582**

[1] Patients classified with antisynthetase syndrome (ASS) where clinical data was not available to stratify by Bohan and Peter classification criteria

Supplementary Table 2 – Method of antibody detection for each positive antibody.

	Immunoprecipitation			Lineblot						
Autoantibody	**UK[1]**	**USA[2]**	**Japan[3]**	**EUROIMMUN Lineblot[4]**	**Other lineblot[5]**	**ELISA**	**Other/Unknown**	**Total positive**	**Number of patients tested[6]**	**Frequency in cohort[7]**
Jo-1	202	49	21	51	4	0	5	**332**	**2,384**	**13.9%**
TIF	73	105	10	5	0	1	3	**197**	**2,053**	**9.6%**
PM/Scl	98	7	11	19	1	0	0	**136**	**2,340**	**5.8%**
Mi2	71	13	5	9	4	0	2	**104**	**2,340**	**4.4%**
NXP2	53	37	1	1	0	1	0	**93**	**1,862**	**5.0%**
cN1A	0	0	0	0	0	46	0	**46**	**302**	**15.2%**
SRP	29	1	4	8	3	0	0	**45**	**2,279**	**2.0%**
HMGCR	0	0	0	0	0	45	7	**52**	**1,394**	**3.7%**
MDA5	27	5	3	0	0	0	0	**35**	**2,076**	**1.7%**
SAE	28	0	2	1	0	0	0	**31**	**1,915**	**1.6%**
PL7	13	3	1	5	1	0	0	**23**	**2,384**	**1.0%**
PL12	5	2	0	3	1	0	0	**11**	**2,384**	**0.5%**

1, Immunoprecipitation conducted by Department of Pharmacy and Pharmacology University of Bath, UK. Includes samples from non-UK cohorts.

2, Immunoprecipitation and confirmation by immunoblotting conducted by Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, OK, USA

3, Immunoprecipitation conducted by Department of Rheumatology and Clinical Immunology, Kyoto University, JP.

4, EUROIMMUN EUROLINE ANA Profile 3, EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (Luebeck, Germany)

5, D-tek PMS8D, PMS12D, SYN10D, MYO7D (Mons, Belgium). ORGENTEC Diagnostika Myositis Plus ORG 760 (Mainz, Germany)

6, Note distribution of testing was not random. For example, anti-cN1A autoantibodies were tested for in a selected cohort of IBM patients.

7, Percentage frequency of antibody present in those tested.

Supplementary Table 3 - Concordance between imputed HLA alleles and next generation sequencing HLA typing for 162 individuals

HLA Locus	2-digit imputation Accuracy	4-digit imputation accuracy
HLA-A	99.70%	98.80%
HLA-B	99.10%	97.50%
HLA-C	100%	99.38%
HLA-DPA1	99.70%	99.40%
HLA-DPB1	98.50%	98.50%
HLA-DQA1	100%	100%
HLA-DRB1	98.4%	96.60%
HLA-DQB1	99.69%	99.38%

Supplementary Table 4 – Frequency of individuals who have at least one copy of HLA-DRB1*03:01, in anti-aminoacyl-tRNA synthetase positive subgroups

Autoantibody	Number	Frequency of HLA-DRB1*03:01
Anti-Jo-1	332	79.2%
Anti-PL7	23	30.4%
Anti-PL12	11	81.8%
Anti-OJ	8	37.5%
Anti-EJ	4	25.0%
Anti-ZO	2	100%
Anti-KS	1	0.00
Controls	1,328	23.0%

Supplementary Table 5 – Raw phased 4-digit HLA alleles for patients with anti-PL7 autoantibodies

	Haplotype 1								Haplotype 2							
	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1
AUS 1	2402	0702	0702	0701	0201	0303	0201	1301	2601	0102	2705	0401	0301	0302	0103	0401
AUS 2	0301	0401	3501	0101	0101	0501	0103	0401	0101	0701	0801	0301	0501	0201	0103	0301
CZE 1	1101	0202	2705	0404	0301	0302	0201	1701	0201	0602	1302	0701	0201	0202	0201	1701
CZE 2	0201	0602	5701	1101	0501	0301	0103	0401	0201	0701	0801	0301	0501	0201	0201	0101
CZE 3	2402	0303	1501	1301	0103	0603	0103	0401	0101	0701	0801	0301	0501	0201	0103	0401
HUN 1	0101	0701	0801	0301	0501	0201	0103	0401	0101	0701	0801	0301	0501	0201	0201	0101
NOR 1	0301	0304	4001	0404	0301	0302	0103	0401	2402	0304	0702	1501	0102	0602	0103	0201
NOR 2	2902	0602	4501	0401	0301	0301	0103	0402	0201	0501	1801	0401	0301	0302	0103	0401
GBR 1	0101	0501	4402	1501	0102	0602	0103	0401	3201	0702	3906	0804	0401	0402	0103	0401
GBR 2	2501	1203	1801	1501	0102	0602	0103	0401	3201	0102	2705	0801	0401	0402	0103	0401
GBR 3	0206	0303	2705	0401	0301	0302	0103	0401	0201	0702	0702	1501	0102	0602	0103	0201
GBR 4	3101	0401	3501	1501	0102	0602	0103	0401	2402	0303	1501	1301	0103	0603	0103	0401
GBR 5	0201	0501	4402	1501	0102	0602	0202	0501	0101	0701	5801	1302	0102	0609	0103	0401
GBR 6	0206	0202	2703	0101	0101	0501	0103	0401	2402	0801	4801	0403	0301	0302	0103	0201
GBR 7	0201	0702	0702	0404	0301	0302	0103	0401	2402	0702	0702	1501	0102	0602	0103	0401
GBR 8	0301	0401	3501	0101	0101	0501	0103	0401	0301	0701	1801	0404	0301	0302	0201	0901
GBR 9	0101	0701	0801	0401	0301	0301	0103	0401	3101	0304	4001	0404	0301	0302	0103	0601
SWE 1	0201	0401	0702	1401	0101	0503	0103	0201	0101	0701	0801	0301	0501	0201	0103	0401
SWE 2	0101	0701	0801	0301	0501	0201	0103	0401	3101	0701	1801	1501	0102	0602	0103	0401
ESP 1	2402	0701	0801	0301	0501	0201	0103	0401	0301	1502	5101	1401	0101	0503	0103	0401
USA 1	0201	0501	4402	0101	0101	0501	0103	0401	0201	0501	4402	0401	0301	0301	0103	0401
USA 2	6802	0401	5301	0102	0101	0501	0201	1401	0101	0701	0801	0901	0301	0303	0103	0401
USA 3	3201	0401	3501	0101	0101	0501	0201	1001	0201	1505	7301	0405	0301	0201	0103	0301

Supplementary Table 6 - Raw phased 4-digit HLA alleles for patients with anti-PL12 autoantibodies

	Haplotype 1								Haplotype 2							
	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1
ITA 1	0301	0501	1801	0301	0501	0201	0103	0301	3002	0401	3502	1104	0501	0301	0103	0402
ITA 2	0201	1203	3901	1601	0102	0502	0103	0401	0201	0202	2705	1303	0501	0301	0103	0301
GBR 1	0201	0702	0702	1101	0501	0301	0103	0401	3002	0501	1801	0301	0501	0201	0103	0402
GBR 2	0301	0702	0702	0801	0401	0402	0103	0301	0301	0702	0702	1101	0501	0301	0103	0201
GBR 3	0101	0701	0801	0301	0501	0201	0201	0101	2402	0702	3906	0404	0301	0302	0103	0402
GBR 4	0301	0701	0801	0301	0501	0201	0103	0402	2402	0102	5601	1302	0102	0604	0103	0401
GBR 5	0101	0702	0702	1301	0103	0603	0103	0401	0101	0701	0801	0301	0501	0201	0103	0401
HUN 1	0101	0701	0801	0301	0501	0201	0103	0402	0201	0704	4402	1601	0102	0502	0103	0401
ESP 1	6801	0501	1801	0301	0501	0201	0103	0202	0301	0401	3501	0403	0301	0302	0103	0201
USA 1	0201	0701	0801	0301	0501	0201	0201	0101	1101	0401	3501	1401	0101	0503	0103	0401
USA 2	0101	0701	0801	0301	0501	0201	0201	0101	0201	0401	3508	1201	0501	0301	0103	0401

Supplementary Table 7 - Raw phased 4-digit HLA alleles for patients with anti-OJ autoantibodies

	Haplotype 1								Haplotype 2							
	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1
GBR 1	0101	0701	0801	0301	0501	0201	0103	0401	3101	0501	4402	0401	0301	0301	0103	0402
GBR 2	0201	0702	0702	1101	0501	0301	0103	0401	2501	1203	1801	1501	0102	0602	0201	1401
GBR 3	0201	0702	0702	0701	0201	0201	0103	0401	0301	0702	0702	1501	0102	0602	0103	0401
GBR 4	0201	1601	5101	1102	0501	0301	0103	0401	3101	0401	3502	0404	0301	0302	0103	2301
GBR 5	2301	0401	4403	0404	0301	0302	0103	0301	0101	0401	3501	1101	0501	0301	0103	0401
GBR 6	0201	0304	1501	0403	0301	0302	0103	0401	0201	0501	4402	0401	0301	0301	0103	0401
SWE 1	0101	0701	0801	0301	0501	0201	0103	0401	0201	0304	4001	0801	0401	0402	0103	0301
USA 1	0201	0303	5501	1401	0101	0503	0201	1001	0101	0701	0801	0301	0501	0201	0103	0301

Supplementary Table 8 - Raw phased 4-digit HLA alleles for patients with anti-EJ autoantibodies

	Haplotype 1								Haplotype 2							
	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1
BEL 1	2402	1502	5101	1101	0501	0301	0103	0401	6801	1203	3801	0301	0501	0201	0103	0401
CZE 1	0201	0102	1501	1301	0103	0603	0202	1901	6601	0702	0702	1501	0102	0602	0103	0402
SWE 1	2402	0701	1801	1501	0102	0602	0103	0401	3101	0303	1501	0804	0401	0402	0103	0401
USA 1	0205	0602	5001	0701	0201	0202	0103	0301	0201	0501	4402	0401	0301	0302	0103	0402

Supplementary Table 9 - Raw phased 4-digit HLA alleles for patients with anti-ZO autoantibodies

	Haplotype 1								Haplotype 2							
	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1
GBR 1	0101	0701	0801	1501	0102	0602	0103	0401	0201	0802	1402	0301	0501	0201	0201	1401
GBR 2	0201	0701	0801	0301	0501	0201	0103	0201	0101	0701	0801	0301	0501	0201	0103	0401

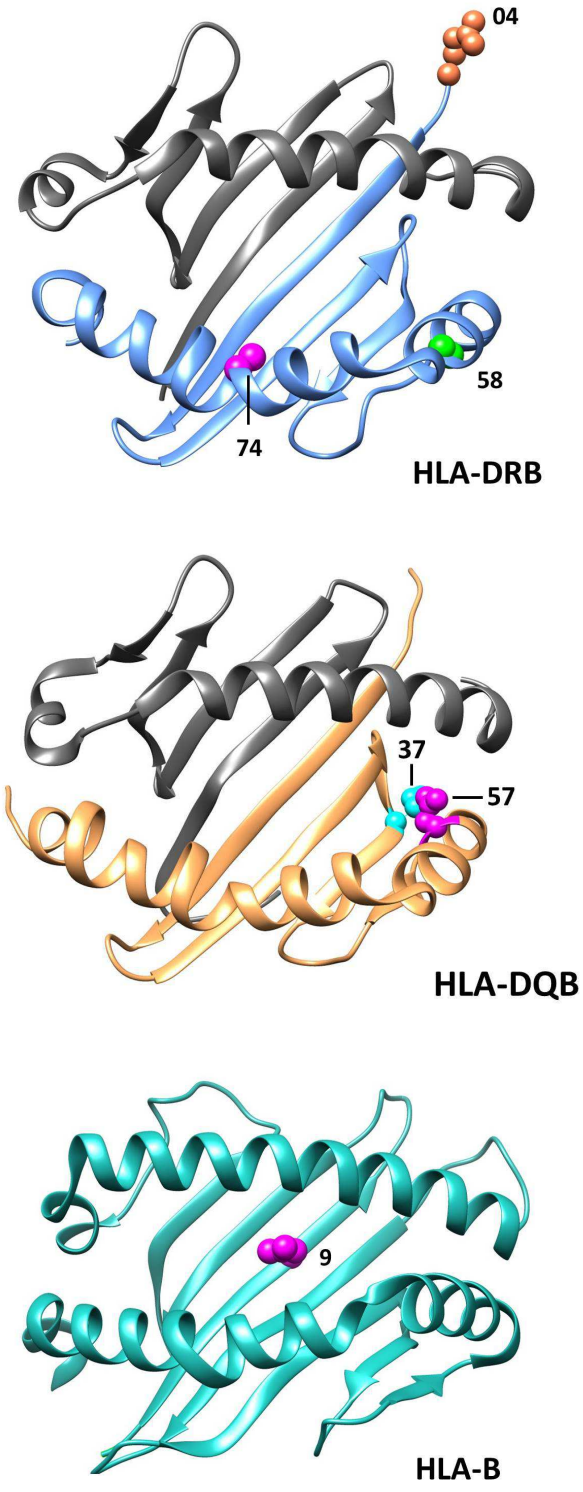
Supplementary Table 10 - Raw phased 4-digit HLA alleles for patients with anti-KS autoantibodies

	Haplotype 1								Haplotype 2							
	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1	A	C	B	DRB1	DQA1	DQB1	DPA1	DPB1
GBR 1	2501	0701	0801	1401	0101	0503	0201	1001	0101	0701	0801	1301	0103	0603	0202	0501

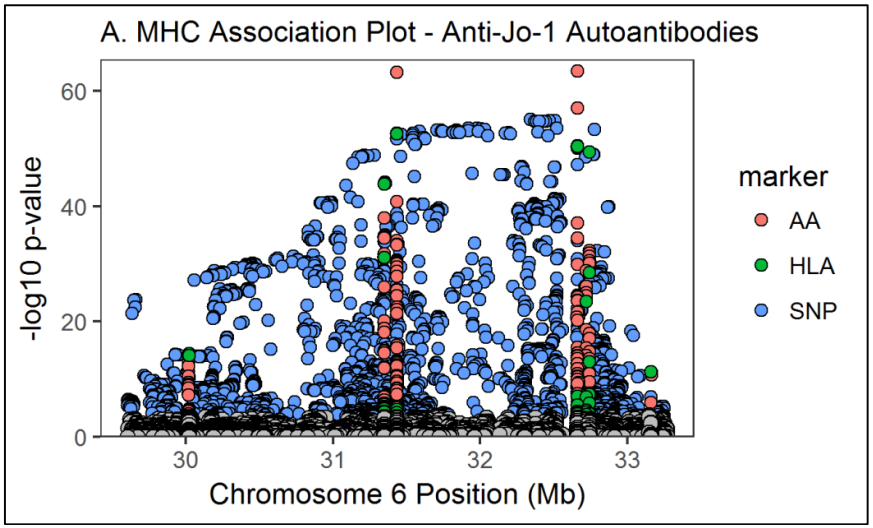
Supplementary Table 11 – Frequencies of alleles in adult- and juvenile-onset IIM patients for anti-Jo-1, anti-PM/Scl, anti-Mi2 and anti-cN1A autoantibodies

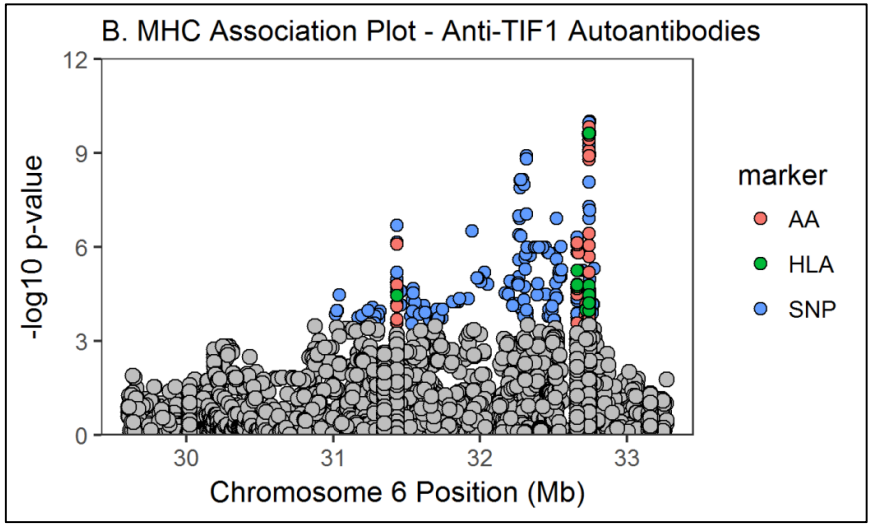
Autoantibody	Allele	Freq in adults, %	Freq in juveniles, %	Freq in controls, %
Jo-1	HLA-B*8:01	243/325 (74.8%)	7/7 (100%)	305/1,328 (23.0%)
PM/Scl	HLA-DQB1*02:01	116/120 (96.6%)	14/16 (87.5%)	133/548 (24.3%)
Mi-2	HLA-DRB1*07:01	59/87 (67.8%)	7/17 (41.2%)	96/416 (23.1%)
cN1A	HLA-DRB1*03:01	35/46 (76.1%)	12/18 (66.7%)	61/256 (23.8%)

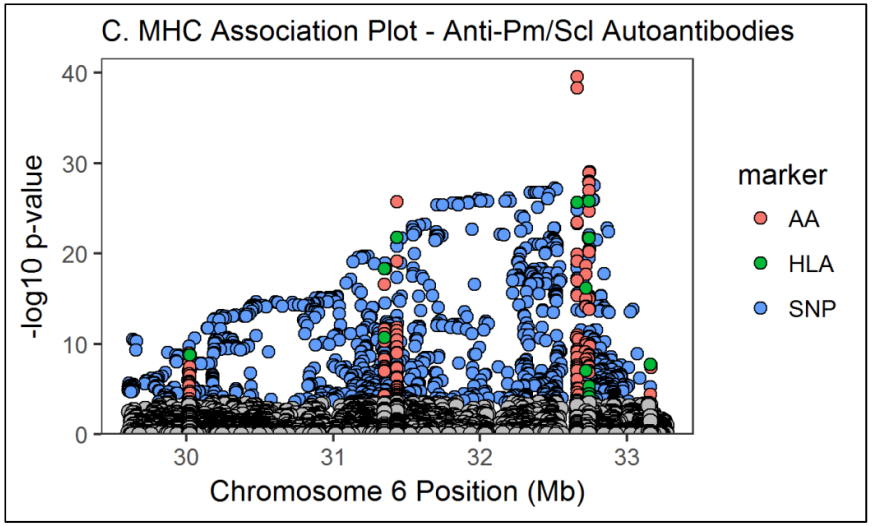
Frequencies as a percentage of individuals heterozygous or homozygous for the risk allele from the combined analysis, stratified by adult and juvenile onset disease.

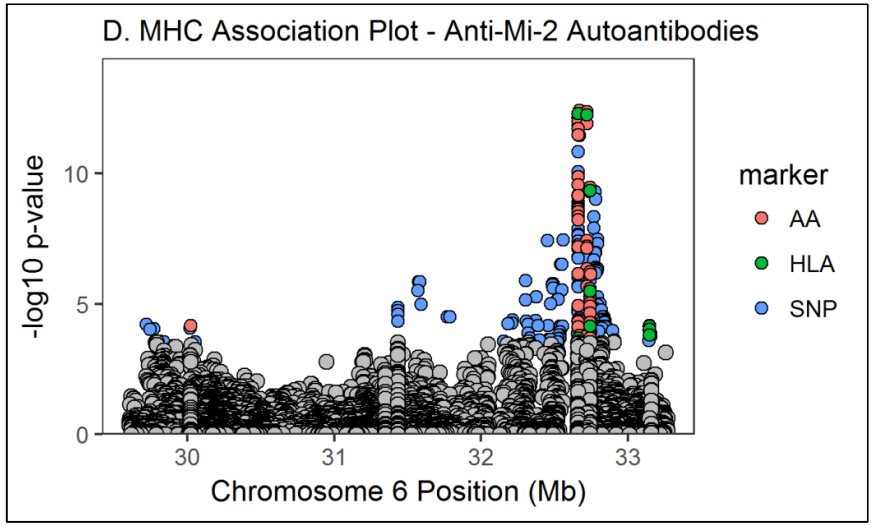


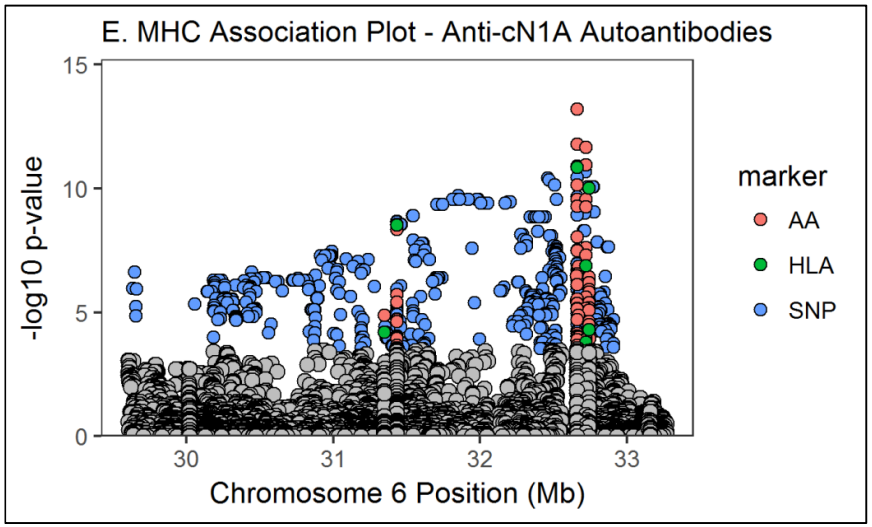
Supplementary Figure 1. The location of associated amino acid positions within the 3D structure of HLA molecules. Protein structures of the HLA peptide binding groove are shown for HLA-DRB (blue) and HLA-DQB (orange) and HLA-B (turquoise). The positions of associated amino acids positions for different IIM autoantibodies are labelled.

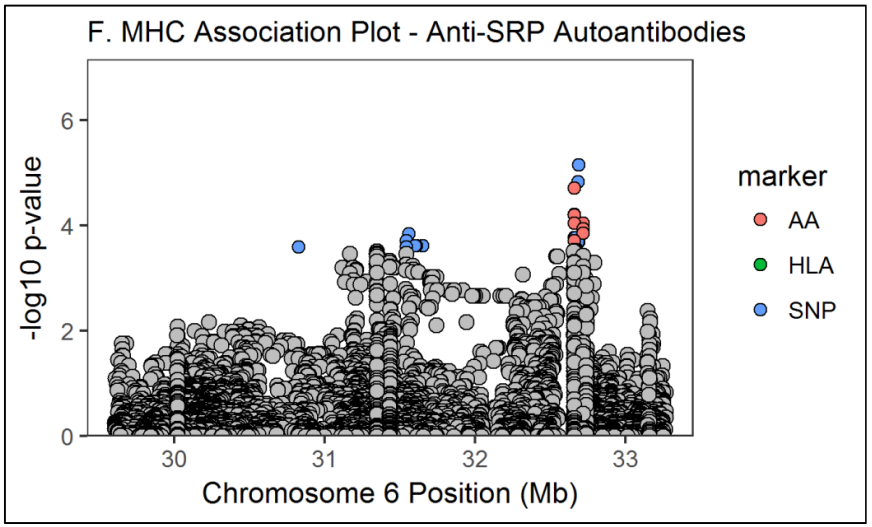

A. MHC Association Plot - Anti-Jo-1 Autoantibodies
-log10 p-value
0
20
40
60
30
31
32
33
Chromosome 6 Position (Mb)
marker
AA
HLA
SNP

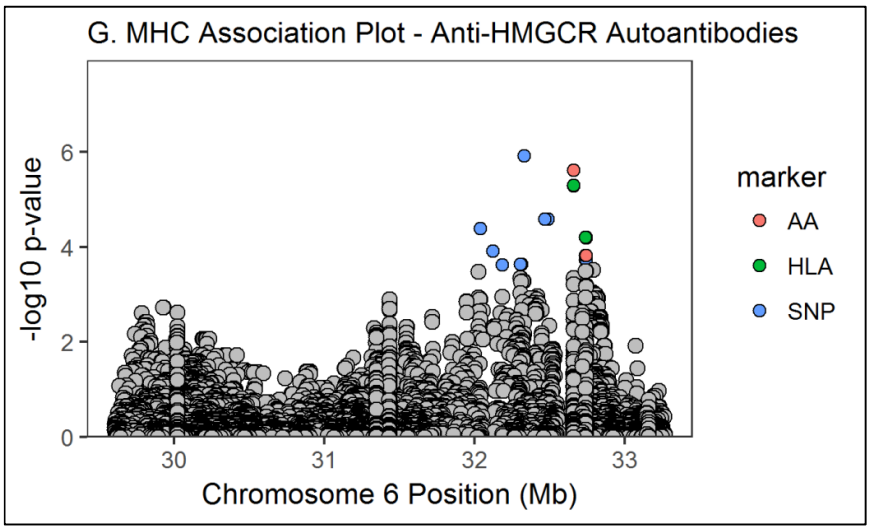

B. MHC Association Plot - Anti-TIF1 Autoantibodies
-log10 p-value
0
3
6
9
12
30
31
32
33
Chromosome 6 Position (Mb)
marker
AA
HLA
SNP

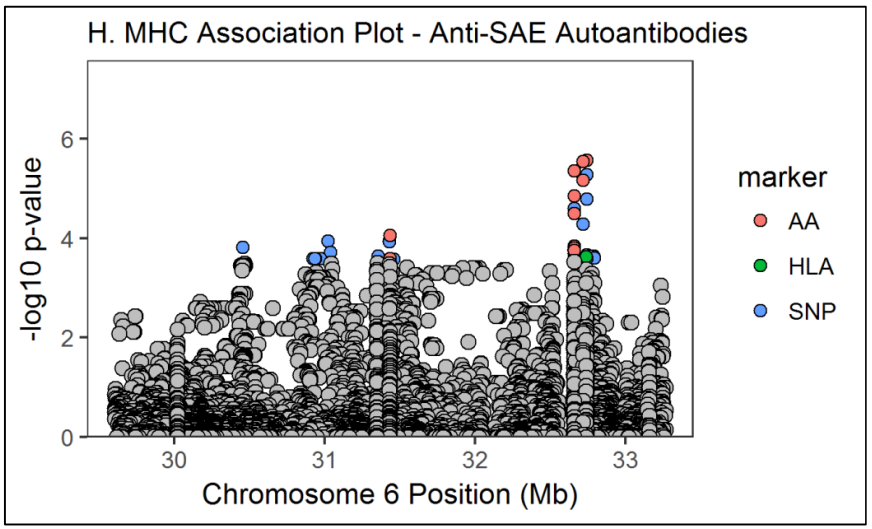

C. MHC Association Plot - Anti-Pm/Scl Autoantibodies
-log10 p-value
0
10
20
30
40
30
31
32
33
Chromosome 6 Position (Mb)
marker
AA
HLA
SNP


D. MHC Association Plot - Anti-Mi-2 Autoantibodies
-log10 p-value
0
5
10
30
31
32
33
Chromosome 6 Position (Mb)
marker
AA
HLA
SNP









Supplementary Figures 2A-H. Regional association plots for autoantibodies with significant associations. Amino acids (AA), classical HLA alleles and SNPs coloured as red, green and blue markers respectively. Non-significant variants are coloured grey ($p>2.9x10^{-5}$). Location of HLA and amino acids plotted by the coordinates of their respective genes.

Supplementary Methods

Autoantibody Testing

Myositis autoantibodies were detected using immunoprecipitation (IP), line-blot, or ELISA, as detailed in Supplementary Table 2.

MSAs (defined as: Jo-1, PL12, PL7, EJ, KS, OJ, Zo, Mi-2, SRP, TIF1, SAE, MDA5, NXP2 and HMGCR) are generally mutually exclusive [15]. 12 individuals with multiple MSAs were removed from the analysis to ensure homogenous subgroups. Anti-Ro was not analysed due to insufficient data on the subunit detected across different cohorts.

In the UK, immunoprecipitation (IP) was conducted in the Department of Pharmacy and Pharmacology, University of Bath, UK as described previously [1]. ELISA was used to confirm anti-TIF1 in those with a 155kDa band and to distinguish anti-MDA5 and anti-NXP2 in those with 140kDa bands. In the USA, IP and confirmatory immunoblotting as appropriate, was conducted by Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, OK, USA [2]. TIF1, NXP2, and MDA5 were confirmed by IP-blotting. In Japan, IP was conducted in the Department of Rheumatology and Clinical Immunology, Kyoto University, JP [3]. ELISAs were used to discriminate other 140kDa bands.

The most common commercially available lineblots used were EUROLINE Myositis Lineblots (Euroimmun, Lübeck, Germany). This consists of a membrane strip with 11 autoantigen assays for the EUROLINE Myositis Profile 3 Lineblot (Ro-52, OJ, EJ, PL-12, PL-7, SRP, Jo-1, PM/Scl75, PM/Scl100, Ku, Mi-2) or 16 autoantigen assays the EUROLINE Myositis 16A lineblot (Mi-2 α, Mi-2 β, TIF1g, MDA5, NXP2, SAE1, Ku, PM/Scl100, PM/Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52). For EUROLINE Immunoblots that include both PM/Scl100 and PM/Scl75 subunits, patients were only considered anti-PM/Scl positive if positive for PM/Scl100 due to suspected false positives with the PM/Scl75 assay [4]. Due to known sensitivity issues with the Mi-2 α and Mi-2 β assays, a more stringent cut-off was required for positivity for this autoantibody [4].

A smaller number of samples were tested using other commercially available lineblots, such as D-tek PMS8D, PMS12D, SYN10D, MYO7D (Mons, Belgium) and ORGENTEC Diagnostika Myositis Plus ORG 760 (Mainz, Germany).

Anti-cN1A was detected in the USA by immunoblot in the Muscle Disease Unit, National Institutes of Health (NIH), MD, USA. Patient sera was used to immunoblot lysates from HeLa cells transfected with full-length cN1A vs. non-transfected HeLa cells [5]. Anti-cN1A was detected in the Netherlands

by ELISA in the Department of Biomolecular Chemistry, University of Nijmegen, NL, using a method described previously [6].

Anti-HMGCR was detected in the USA by ELISA followed by IP at the Muscle Disease Unit, National Institutes of Health (NIH), MD, USA [7], in the UK by ELISA in the Department of Pharmacy and Pharmacology, University of Bath, UK [8], by addressable laser bead immunoassay (ALBIA) in France at the Department of Immunology, Rouen University Hospital, FR [9].

HLA Modelling

Molecular graphics images were produced using the UCSF Chimera package (v1.10.1) from the Computer Graphics Laboratory, University of California, San Francisco (supported by NIH P41 RR-01081).

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