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HLA-A*26:01 is associated with vertebral endplate bone marrow lesions (Modic changes): host immunogenetic susceptibility linked to systemic adaptive immunity

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HLA-A*26:01 is associated with vertebral endplate bone marrow lesions (Modic changes): host immunogenetic susceptibility linked to systemic adaptive immunity

Abstract

Purpose: Modic changes (MC) are vertebral endplate bone marrow lesions associated with chronic low back pain. Mechanical and inflammatory triggers of MC are well studied, but host immunogenetic susceptibility remains poorly understood. Given the accumulation of T cells in MC lesions, we investigated the association of MC with human leukocyte antigen (HLA) alleles.

Methods: We studied HLA association with MC across three independent samples with MC scoring (n=324, n=657, and n=1092). Associated alleles were compared with ancestry-matched population reference data (n=9634-9936). In the first sample, we also profiled CD8 T cells by spectral flow cytometry (n=191) and analysed the T cell receptor β (TCRβ) repertoire from whole-blood RNA sequencing (n=317).

Results: HLA-A*26:01 was a risk allele for MC (odds ratio, OR 2.24, 95% confidence interval, CI 1.18–4.24, false discovery rate, FDR=0.040) and was enriched in participants with MC against population reference data (OR 1.95, 95% CI 1.13–2.95, FDR=0.009). HLA-A*26:01 had an age-dependent effect (likelihood ratio test p=0.005). HLA-A*26:01 carriers with MC had a 1.27-fold expanded $CD28^{+}CD127^{+}PD\text{-}1^{+}CD39^{+}NKG2D^{+}$ memory CD8 T cell population (95% CI 1.01–1.60, p=0.044) and lower TCRβ clonality (0.79-fold, 95% CI 0.67–0.94, p=0.007).

Conclusion: HLA-A*26:01 is associated with age-dependent MC susceptibility and distinct circulating CD8 T cell and TCR repertoire profiles. These findings suggest that MC pathogenesis involves host immunogenetic susceptibility and systemic adaptive immunity, beyond local pathological triggers.

Keywords: Modic changes; HLA-A*26:01; human leukocyte antigen; low back pain; CD8 T cells; T cell receptor repertoire

Introduction

Lumbar vertebral endplate bone marrow lesions called Modic changes (MC) [1, 2] are common in people with chronic low back pain (cLBP). MC are classified into three types by magnetic resonance imaging (MRI) signal[1] (**Fig. 1**). MC1 and MC2 are interconvertible, and both may evolve into MC3, suggesting an active and progressive pathological process[3].

MC have primarily been investigated in relation to mechanical endplate damage and local inflammatory triggers including sterile inflammation and low-virulent disc infection[3–6]. MC marrow shows increased vascularisation, innervation, immune cell infiltration and inflammatory mediators[3], and is enriched for T- and B-cell signatures[6]. Animal models further support the role of T cells in MC[4, 5]. These findings implicate adaptive immunity in MC pathogenesis. Genetic studies also indicate inherited susceptibility to MC, but whether it involves genes relevant to adaptive immunity remains unknown[7]. Human leukocyte antigen (HLA) molecules present peptides to conventional T cells and are central to adaptive immunity[8]. Specific HLA alleles are strongly associated with susceptibility to many immune-mediated diseases[9], but whether HLA variation is associated with host susceptibility to MC remains unknown. Systemic immune alterations have also been reported in MC, but their relationship to host immunogenetics remains unknown[10].

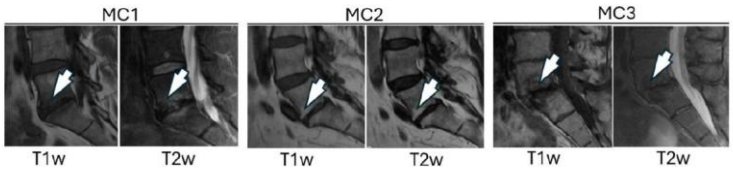


Fig. 1 The three types of Modic changes. T1- and T2-weighted MRI of type 1, 2 and 3 Modic changes (MC1–MC3)

Methods

We tested the hypothesis that carriage of specific HLA alleles is associated with lumbar MC.

Subjects and data

We utilised three samples with lumbar MC scoring: the University of California, San Francisco comeBACK sample (UCSF) of the NIH Back Pain Consortium Research Program (BACPAC), the Northern Finland Birth Cohort 1966 (NFBC1966), and the United Kingdom Adult Twin Registry (TwinsUK). In UCSF, 324 participants had blood transcriptomes passing quality control and a clinical MRI (Supplementary Methods S1.1, Online Resource 1). T cell receptor β (TCRβ) repertoires were assembled for 317 of them. Spectral flow cytometry data for 191 came from a previous study on this sample[10]. From NFBC1966 and TwinsUK we included participants with MC classification and HLA alleles imputed from genome-wide association study (GWAS) genotypes, 1092 and 657 respectively. Reference frequencies of HLA-A*26:01 (eleven samples, n=9634) and HLA-A*11:01 (twelve samples, n=9936) came from U.S. samples rated gold standard in the Allele Frequency Net Database (allelefrequencies.net), ancestry-matched to UCSF (Supplementary Methods S2.3). The TwinsUK pain analysis, which did not require MRI, included 3943 participants, 406 with severe pain (Supplementary Methods S1.2.1). Ancestry (five continental super-populations) was inferred from RNA sequencing (RNA-seq) in UCSF and from GWAS principal components in TwinsUK (Supplementary Methods S2.1). BMI, sex and smoking status were recorded at the MRI visit, or, for the pain analysis, at the visit closest to the pain assessment. MC were graded by established definitions on sagittal T1- and fat-saturated T2-weighted lumbar MRI in UCSF, T1- and T2-weighted MRI in NFBC1966 and sagittal T2-weighted MRI in TwinsUK (Supplementary Methods S1).

Statistical analysis

MC status was dichotomised. HLA alleles were analysed at four-digit resolution as carrier status, with imputed carriage in NFBC1966 and TwinsUK requiring a posterior probability≥0.9 (Supplementary Methods S2.2). Alleles carried by<2.5% of a sample were not tested. Association of carriage with MC was tested by logistic regression adjusted for age, BMI, sex, smoking and ancestry (odds ratio, OR, with 95% confidence interval, CI). TwinsUK models included family as a random effect, and Firth penalisation was used for separation. Alleles present in all three samples were pooled by random-effects meta-analysis, with heterogeneity assessed by Cochran's Q and I^2 and direction-aligned p-values combined by Stouffer's method. Benjamini–Hochberg (BH) correction (false discovery rate, FDR) was applied within each gene. Linkage disequilibrium (LD) was quantified as Rogers–Huff r^2, primarily on the 57 alleles with estimates in all three samples. For external validation, published reference frequencies were expanded into ancestry-matched individual carrier records. These were analysed with UCSF data by mixed-effects logistic regression (source and ancestry fixed, study random), separately in participants with and without MC (Supplementary Methods S2.3).

In UCSF and TwinsUK, a carriage × age interaction term (age centred at the mean, per decade) was added to the association model and tested by likelihood ratio. ORs were pooled by fixed-effect meta-analysis and likelihood ratio p-values by Stouffer's method. Marginal standardised probabilities, risk differences and age-specific ORs were derived from these models (Supplementary Methods S2.4). Severe cLBP (intensity≥6/10) was modelled against HLA-A*26:01 carriage, adjusted for sex, BMI, smoking and, in TwinsUK, age. Firth regression was used in NFBC1966 and family-clustered robust standard errors in TwinsUK, with pooling by fixed-effect meta-analysis.

T cell receptor β variable (TRBV) genes encode the variable region of the TCR β-chain, which contributes to peptide–HLA recognition. TRBV usage can therefore reflect, in part, HLA-dependent thymic selection and subsequent antigen-driven clonal expansion. TRBV usage and the clonal structure of the CDR3β repertoire were reconstructed from blood RNA-seq data with TRUST4 v1.1.11.

Repertoires were rarefied to 250 productive reads over 200 draws and summarised by clonality and diversity indices (Supplementary Methods S2.5). Both were analysed with a Gamma generalised linear model (GLM) (log link, HC3 standard errors) adjusted for age, sex and BMI. Log sequencing depth was added for clonality and MC status in the all-participant TRBV model, with BH correction across genes. TRBV usage was also tested for a carriage × MC interaction. The age effect on clonality was estimated in non-carriers, adjusted for sex and BMI.

$CD8^+$ αβ T cells were identified by spectral flow cytometry, gated manually in FlowJo as $CD3^+CD8a^+CD4^-$ after excluding γδ (TCRpanγδ, Vδ1, Vδ2, Vγ4 or $V\gamma9^+$) and MAIT ($TCRV\alpha7.2^+CD161^+$) cells[10]. 2000 cells were sampled per donor (219 donors, 191 with HLA typing and covariates). They were clustered with FlowSOM on CD45RA, CCR7, CD28, CD127, PD-1, HLA-DR, CD39, CD73, CD26, CD56, NKG2D, CD7, CD161, CD24, CD16 and CD11a into three metaclusters, the largest stable partition by bootstrap Jaccard (Supplementary Methods S2.6). B cells were gated as $CD19/CD20^+CD3^-$. Compartment sizes, metacluster abundance and repertoire indices were compared across the three groups in one Gamma GLM per outcome, adjusted for age, sex and BMI; a trend (groups coded 0–2) was tested separately.

Analyses were done using R 4.6 and Python 3.11. Claude (Anthropic) was used for coding assistance.

Results

HLA-A*26:01 associates with increased, and HLA-A*11:01 with decreased MC risk

Across the three samples (**Tab. 1**, **Tab. S1**, Online Resource 2), 81–107 HLA alleles were tested (**Fig. S1a–c**, Online Resource 1, **Tab. S2**), and 67 were tested in all three (**Fig. 2a**, **Tab. S3**). Random-effects meta-analysis identified HLA-A*26:01 as associated with increased MC risk (OR 2.24, 95% CI 1.18–4.24, Stouffer FDR=0.040) (**Fig. 2b,c**). HLA-A*11:01 was protective (OR 0.58, 95% CI 0.38–0.91, Stouffer FDR=0.040) (**Fig. 2b,d**, **Tab. S3**).

HLA alleles are often co-inherited, so an association can belong to a haplotype rather than to the allele tested. No allele was strongly linked to either HLA-A*26:01 or HLA-A*11:01. Across the 57 alleles with LD estimates in all three samples, the highest r^2 was 0.17 with HLA-A*26:01 and 0.07 with HLA-A*11:01, and at most 0.26 on the full sample-specific panels. Both were therefore analysed individually.

Table 1 Characteristics of participants in the three samples

	UCSF			TwinsUK			NFBC1966		
	Without MC	**With MC**	**p**	**Without MC**	**With MC**	**p**	**Without MC**	**With MC**	**p**
Participants, n	113	211		400	257		552	540	
Age (years)	47.7 ± 17.0	58.2 ± 13.6	<0.001	55.7 ± 9.7	61.2 ± 8.4	<0.001	46.3 ± 0.4	46.4 ± 0.4	0.003
Body mass index (kg/m²)	25.6 ± 4.1	27.0 ± 5.0	0.008	25.5 ± 5.0	26.3 ± 4.8	0.066	25.9 ± 4.0	27.0 ± 4.6	<0.001
Female sex	70 (61.9%)	116 (55.0%)	0.275	391 (97.8%)	243 (94.6%)	0.048	322 (58.3%)	255 (47.2%)	<0.001
Smoking status			0.005			0.012			0.208
Never	87 (77.0%)	124 (58.8%)		247 (61.8%)	134 (52.1%)		299 (54.2%)	270 (50.0%)	
Former	23 (20.4%)	77 (36.5%)		57 (14.3%)	34 (13.2%)		170 (30.8%)	165 (30.6%)	
Current	3 (2.7%)	10 (4.7%)		96 (24.0%)	89 (34.6%)		69 (12.5%)	86 (15.9%)	
Predicted ancestry			0.466			1			
European	72 (63.7%)	153 (72.5%)		400 (100%)	257 (100%)		n/a	n/a	
East Asian	16 (14.2%)	20 (9.5%)		0	0		n/a	n/a	
Admixed American	15 (13.3%)	19 (9.0%)		0	0		n/a	n/a	
African	6 (5.3%)	12 (5.7%)		0	0		n/a	n/a	
South Asian	4 (3.5%)	7 (3.3%)		0	0		n/a	n/a	

Values are mean ± standard deviation for continuous variables and count (percentage) for categorical variables, with p values from Welch's t-test and the chi-square test, respectively. NFBC1966 smoking status was unknown for 14 participants without MC and 19 with MC. n/a, not available.

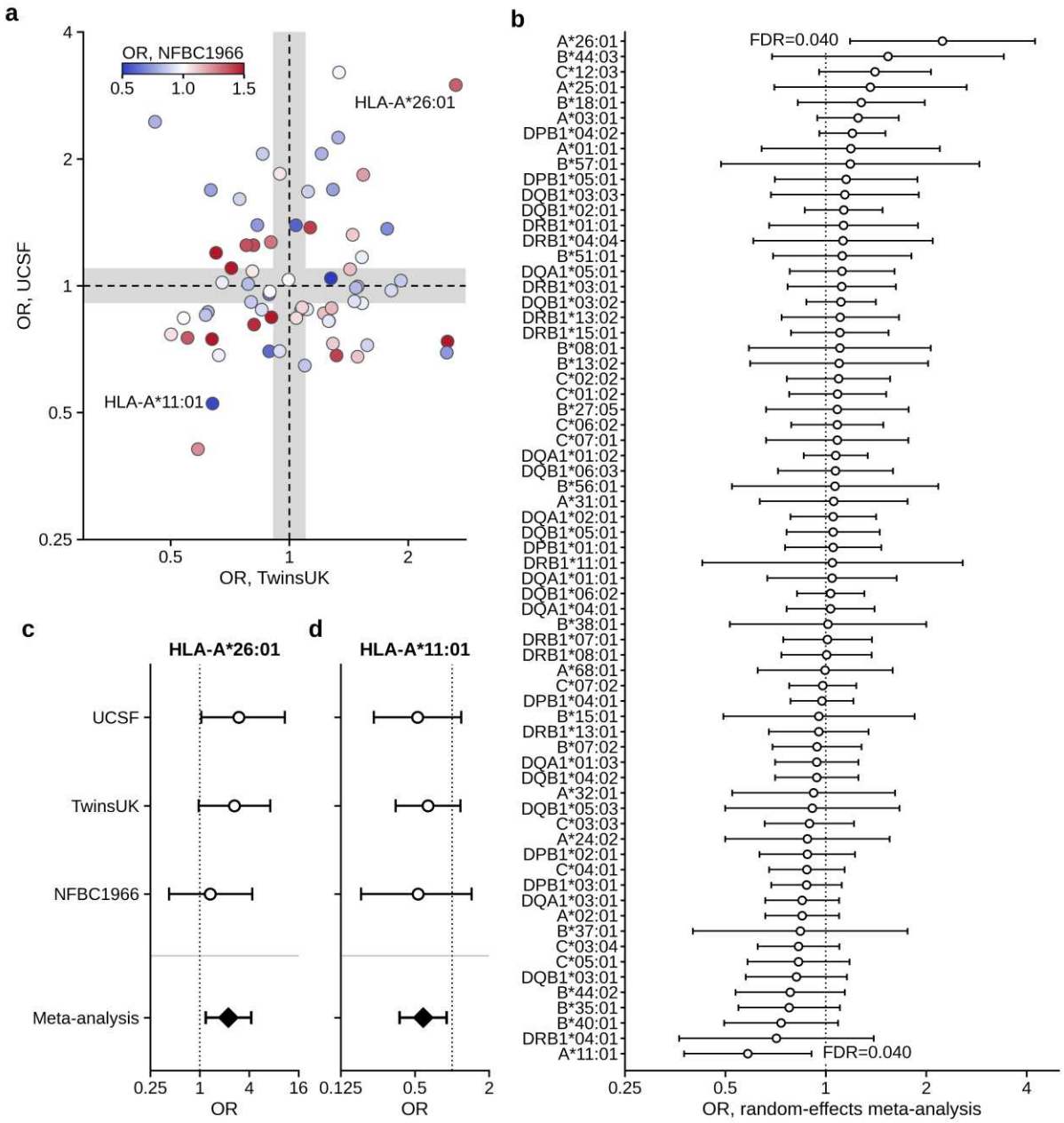


Fig. 2 HLA-A*26:01 increases and HLA-A*11:01 decreases the risk of MC across three samples. a) OR per allele in UCSF (y-axis) against TwinsUK (x-axis), coloured by the NFBC1966 OR; grey area, effect size of 10%. b) Random-effects meta-analysis of the 67 alleles tested in all three samples, with Stouffer FDR for the significant alleles. c) Per-sample ORs for HLA-A*26:01 with the random-effects meta-analysis (diamond). d) The same for HLA-A*11:01. Error bars in all figures are 95% CI

HLA-A*26:01 is enriched in participants with MC against population reference data

Against ancestry-matched U.S. reference data (**Tab. S4**), HLA-A*26:01 was more frequent in participants with MC than in the general population (OR 1.95, 95% CI 1.13–2.95, FDR=0.009), but not in participants without MC (OR 0.62, 95% CI 0.14–1.29, FDR=0.398) (**Fig. 3a,b**). HLA-A*11:01 did not differ from the reference population with or without MC (**Fig. 3c,d**). Across UCSF and the reference data, HLA-A*26:01 was less frequent in participants of African ancestry, and HLA-A*11:01 less frequent in admixed American and more frequent in Asian ancestry (**Fig. 3**, **Tab. S4**).

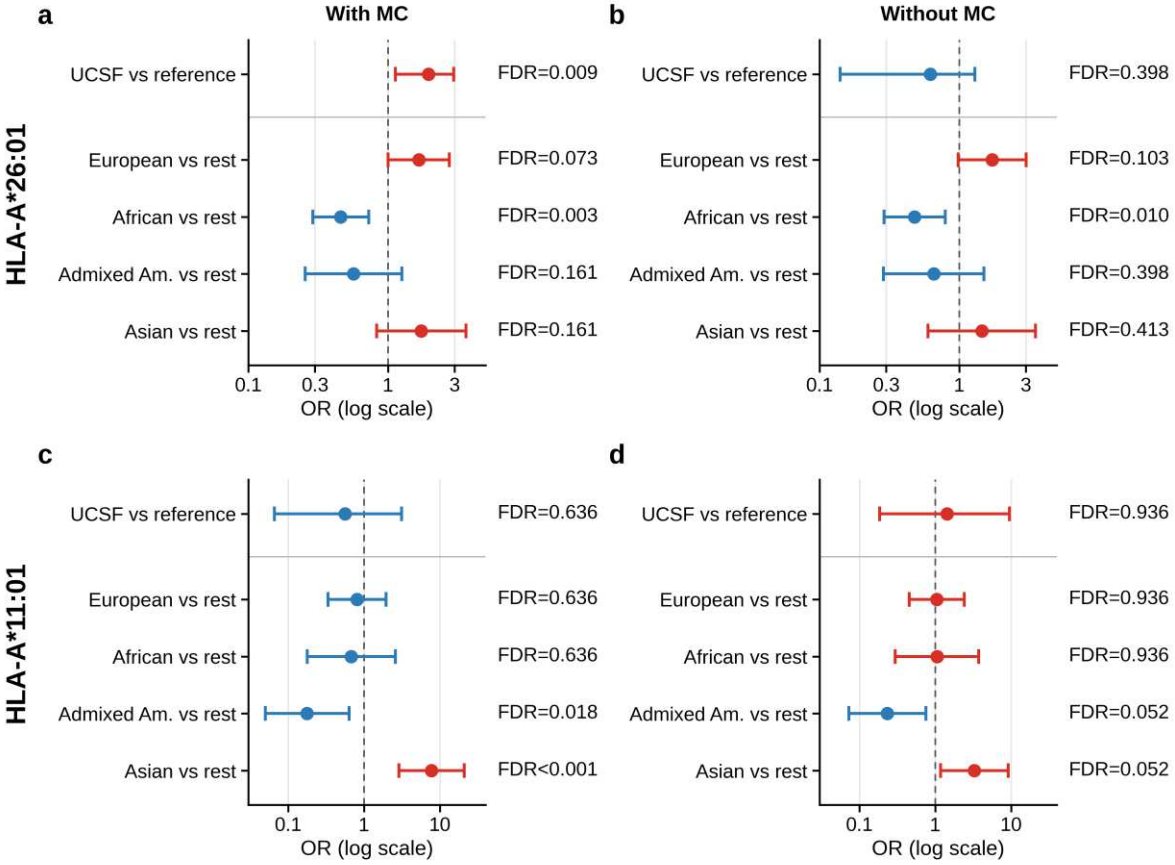


Fig. 3 HLA-A*26:01 is enriched in UCSF participants with MC against population reference data. In each panel the first row compares UCSF with ancestry-matched U.S. population reference data and the rows below compare each ancestry group with the other ancestry groups across UCSF and the reference data combined, adjusted for source. Error bars, 95% CI. a) HLA-A*26:01 in participants with MC. b) HLA-A*26:01 in participants without MC. c) HLA-A*11:01 in participants with MC. d) HLA-A*11:01 in participants without MC

HLA-A*26:01 amplifies age-related risk of MC

HLA-A*26:01 had similar OR in UCSF and TwinsUK but a markedly smaller effect in NFBC1966 (**Fig. 2c**). All NFBC1966 participants were examined at age 46, while the other samples span adult life with older mean ages. We thus examined how the candidate alleles impact age-related MC risk (**Fig. 4**). Carrier and non-carrier probability curves for HLA-A*26:01 were similar at younger ages and diverged progressively at older ages, with carriers approaching 100% (**Fig. 4a–b**, **Tab. S5**). Age-specific ORs crossed 1 at age 43.4 (OR 1.01, 95% CI 0.30–3.29), and the lower confidence limit first exceeded 1 at age 53.5 (OR 2.63, 95% CI 1.00–6.75). The OR reached 24.36 (95% CI 1.87–348.35) at age 79 (**Fig. 4c**, **Tab. S5**). Age was strongly associated with MC (meta-analysis OR per 10-year increase 1.61, 95% CI 1.40–1.85, p<0.001). HLA-A*26:01 modified this effect (meta-analysis OR for carriage × 10 years 2.87, 95% CI 0.98–8.37, p=0.054; likelihood ratio p=0.005), raising the allele effect at the mean age to OR 3.70 (95% CI 1.32–10.39), p=0.013 (**Fig. 4d**, **Tab. S5**). The different ages of the samples (**Fig. 4e**) can therefore explain their different ORs (**Fig. 2c**). At the matched age of 46 the ORs were consistent across samples: UCSF 1.35, TwinsUK 1.30 and NFBC1966 1.34 (**Fig. 4f,g**). HLA-A*11:01 showed no interaction with age (OR for carriage × 10 years 1.04, 95% CI 0.67–1.60, p=0.861) (**Fig. 4h–k**, **Tab. S5**).

We tested carriage against severe cLBP (intensity≥6 on a 0–10 scale), a pre-specified phenotype associated with MC[11]. The estimate pooled across NFBC1966 and TwinsUK showed no association (OR 0.68, 95% CI 0.39–1.21, p=0.188) (**Fig. S2**, **Tab. S6**).

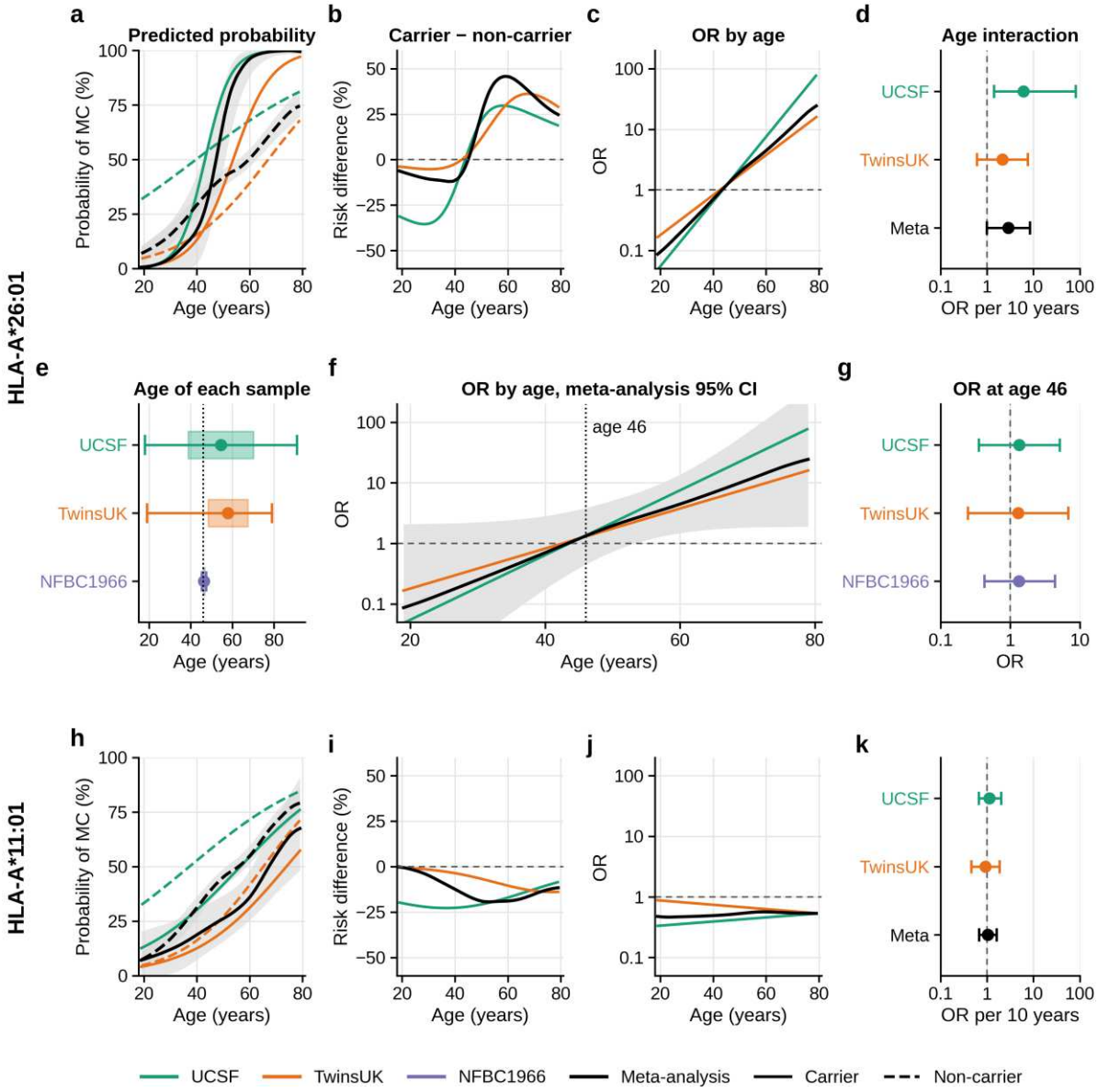


Fig. 4 HLA-A*26:01 amplifies the age-related risk of MC. HLA-A*26:01, a–g; HLA-A*11:01, h–k. a) Predicted MC probability in carriers and non-carriers. b) Absolute risk difference. c) Age-specific OR. d) OR for the carriage × age interaction. e) Age of each sample, mean ± SD and range. f) Age-specific OR with the meta-analysis 95% CI. g) OR per sample at age 46. h) Predicted MC probability in carriers and non-carriers. i) Absolute risk difference. j) Age-specific OR. k) OR for the carriage × age interaction

HLA-A*26:01 carriers with MC have more NKG2D$^+$ memory CD8 cells, different TRBV usage and lower TCR clonality

Because HLA-A presents peptides to CD8$^+$ αβ T cells, we compared their abundance, phenotype and clonality in HLA-A*26:01 carriers with MC on a subset of the UCSF sample (**Tab. S7**). The size of the B cell, T cell and CD8$^+$ αβ T cell compartments did not differ in HLA-A*26:01 carriers with MC (**Fig. 5a**). Clustering of 438,000 CD8$^+$ αβ T cells gave three stable metaclusters (**Fig. S3**, **Fig. 5b**). One of them, C2 (CD28$^+$CD127$^+$PD-1$^+$CD39$^+$NKG2D$^+$CD45RA$^-$), was 1.27-fold more abundant in A*26:01

carriers with MC than in non-carriers without MC (95% CI 1.01–1.60, p=0.044) (**Fig. 5c,d**). Non-carriers with MC fell between the two without separating from either (trend p=0.047) (**Fig. 5c**).

CDR3β assembly from the same RNA-seq data gave a median of 725 productive reads and 286 clonotypes per participant. Among non-carriers, clonality increased with age (×1.08 per decade, p<0.001). Carriers with MC had a less clonal repertoire than non-carriers without MC (0.79-fold, 95% CI 0.67–0.94, p=0.007) or non-carriers with MC (0.79-fold, 95% CI 0.66–0.93, p=0.006) (**Fig. 5e**). The reduction was concentrated in the largest clones. Carriers with MC held a smaller share of reads in their top 5% of clonotypes (0.90-fold, 95% CI 0.83–0.98, p=0.015), and the deficit shrank towards unity as smaller clones were added (**Fig. S4a,b**, Supplementary Results S3.1).

TRBV usage depended on both HLA-A*26:01 carriage and MC. Across all participants, carriers used less TRBV11-1 (0.69-fold, 95% CI 0.59–0.81, FDR<0.001) and TRBV7-6 (0.80-fold, FDR=0.027), with nominally lower TRBV15 (0.80-fold, p=0.013) and TRBV6-6 (0.87-fold, p=0.050) (**Fig. 5f**). Among participants without MC, carriers used less TRBV6-6 (0.73-fold, FDR<0.001) and more TRBV14 (1.89-fold, FDR=0.004) (Fig. 5f). Among participants with MC, carriers used less TRBV11-1 (0.68-fold, FDR=0.002), TRBV15 (0.73-fold, FDR=0.029) and TRBV7-6 (0.78-fold, FDR=0.045), and TRBV14 reversed to nominally lower usage (0.77-fold, p=0.014) (**Fig. 5f**). Carriers with MC also overused TRBV7-9 (1.10-fold, p=0.028). Lesion status modified the carriage effect for TRBV14 (interaction p<0.001), TRBV15 (p=0.006), TRBV30 (p=0.007) and TRBV6-6 (p=0.025), but not for TRBV11-1 (p=0.51) or TRBV7-6 (p=0.17). The interaction for TRBV7-9 was marginal (p=0.052; Supplementary Results S3.2).

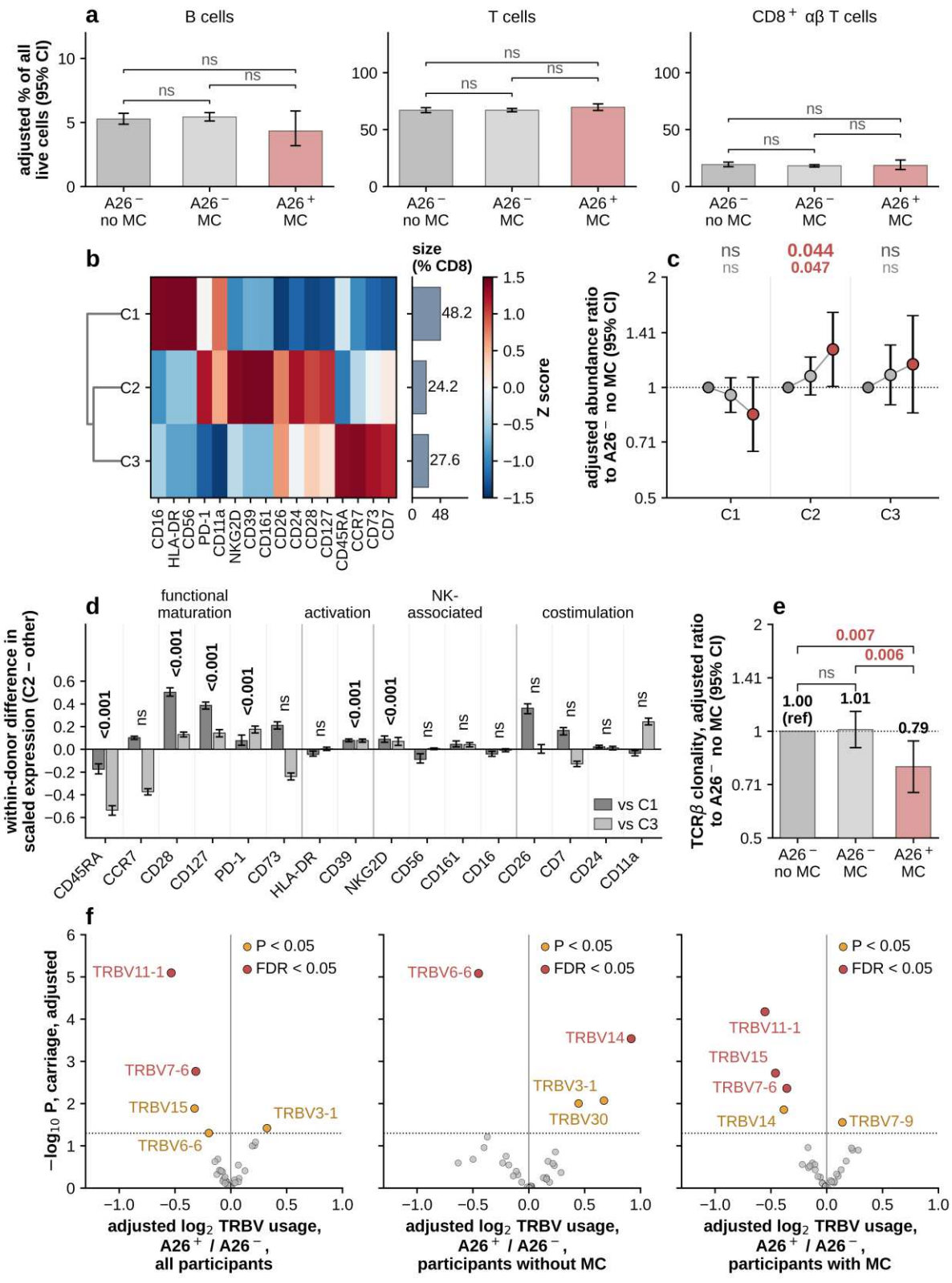


Fig. 5 HLA-A*26:01 carriers with MC have an expanded memory CD8 T cell population, lower TCR clonality and different TRBV usage a) B cells, T cells and CD8⁺ αβ T cells as adjusted share of live cells. b) Z-scored marker profiles of the three CD8 metaclusters and their share of CD8 T cells. c) Metacluster abundance relative to A*26:01-negative participants without MC. Upper value represents P for carriers with MC versus non-carriers without MC; lower value is trend across groups. d) Within-donor difference between C2 and the other metaclusters for the 16 clustering markers (bars, mean;

whiskers, IQR); P, intersection-union test that C2 differs from both by >0.05 in the same direction. e) TCRβ clonality on the same ratio scale. f) TRBV usage in carriers versus non-carriers in all participants (left), participants without MC (middle) and participants with MC (right). Error bars (a, c, e), 95% CI; ns, p≥0.05

Discussion

We identified HLA-A*26:01 as a reproducible genetic risk allele for MC across three independent samples, confirmed against population reference data. This first immunogenetic association with MC indicates that adaptive immunity contributes to MC susceptibility in a genetically defined subset of individuals.

CD8 T cell signatures are enriched in MC lesions[6], and HLA class I molecules present intracellular peptides to CD8 T cells[8]. Specific HLA class I alleles are already known to confer risk of other immune-mediated inflammatory musculoskeletal diseases such as ankylosing spondylitis, psoriatic arthritis or Behçet's disease[9, 12]. HLA-A*26:01 is among the alleles associated with Behçet's disease[12]. The MC association with HLA-A*26:01 is strongly age-dependent: carriers and non-carriers differ little before the mid-40s, after which carrier risk rises steeply. This pattern suggests that HLA-A*26:01 may modify MC susceptibility in the context of age-related processes, potentially including endplate damage, rather than independently initiating the lesion. Lifelong damage to endplates and intervertebral discs (IVDs) may expose normally immune-privileged IVD tissue[13] to immune cells through vascularisation of the damaged IVD[14], or allow bacterial infiltration and dysbiosis[15]. Some bacteria survive within IVD cells[16], and strains detected in MC-associated IVDs strongly upregulate HLA class I molecules on IVD cells (unpublished data). Presentation of intracellular bacterial antigens could thus drive exaggerated CD8 T cell activation in HLA-A*26:01 carriers.

HLA molecules shape the TCR repertoire[17], and HLA-A*26:01 carriage appears to influence it at two levels: through MC-independent differences in TRBV usage and through differences associated with MC status. TRBV11-1 is reduced in carriers regardless of lesion status, likely reflecting HLA-A*26:01-dependent thymic selection[18]. Other genes track the lesion instead, and TRBV14 is the clearest example: carriers without MC use it more, carriers with MC use it less. Thymic selection alone cannot explain this reversal, suggesting that MC-associated processes also shape the TCR repertoire. HLA-B*27-positive ankylosing spondylitis and acute anterior uveitis patients overuse the same variable gene, TRBV9, providing an example that a single class I allele can bias TRBV usage in the context of musculoskeletal disease[19]. A*26:01 may likewise shape which TCRs the repertoire contains, while MC-associated processes may further modify its composition. Carriers with MC also have a less clonal circulating repertoire than expected for their age, similarly as reported in ankylosing spondylitis[20]. Their memory CD8 population expressing increased levels of CD28, CD127, PD-1, CD39, and NKG2D but less CD45RA is modestly expanded. These surface proteins suggest activation (CD39)[21], an effector memory phenotype ($CD45RA^{-}$, CD28, CD127, PD-1)[22] and the capacity to recognise and potentially kill stressed autologous cells (NKG2D)[23]. Together, these findings show that HLA-A*26:01 carriers with MC have measurable alterations of circulating T cells.

Antibiotic trials in MC1 have shown mixed efficacy[24, 25], likely reflecting heterogeneous pathobiology. Host immunogenetics may complement local pathological features in defining MC subgroups for future treatment-response studies. Although HLA-A*26:01 was associated with MC, we found no significant association with severe cLBP, leaving its relevance to pain unresolved. Whether HLA-A*26:01 can improve individual risk prediction or inform preventive strategies remains to be established.

Limitations

Residual confounding by lifestyle, unknown comorbidities or environmental exposures cannot be excluded. HLA alleles in NFBC1966 and TwinsUK were imputed rather than directly typed, and imaging protocols and MC scoring differed between samples. Antigen specificity and HLA-dependent T cell activation remain to be demonstrated.

Conclusion

We identified HLA-A*26:01 as the first HLA risk allele for MC, with an association that strengthens with age. Expansion of circulating memory CD8 T cells and altered TCR repertoires in the blood of HLA-A*26:01 carriers with MC indicate systemic involvement of adaptive immunity. These findings extend current models of MC pathogenesis by identifying host immunogenetic susceptibility as an additional dimension alongside local mechanical and inflammatory triggers.

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Online Resources

Online Resource 1 Supplementary methods and results, Fig. S1–S4

Online Resource 2 Tab. S1–S7

Supplementary Files

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