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Genetic biomarkers of clinical manifestations in giant cell arteritis define distinct patient subgroups

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ABSTRACT

Objectives. Giant cell arteritis (GCA) is a clinically heterogeneous disease, which complicates both diagnosis and management. This study aimed to identify genetic risk factors associated with GCA clinical manifestations and evaluate their utility for defining clinical phenotypes.

Methods. Genome-wide genotype data from 3,498 patients with GCA and 15,550 controls were analyzed to investigate the genetic architecture of GCA manifestations. Logistic regression was used to compare patients with and without each manifestation, as well as each subgroup of patients versus controls. Gene annotation was conducted based on functional information using FUMA. Latent class analysis (LCA) was applied to evaluate the ability of associated variants to classify GCA patients into genetic subgroups.

Results. We identified seven human leukocyte antigen (HLA) variants specifically associated with different clinical features. Furthermore, seven non-HLA associations across six clinical manifestations were found. Gene prioritization highlighted biologically relevant candidate genes for GCA pathogenesis, including *IL17A* (limb claudication) and *IL22RA1* (jaw claudication), both involved in the Th17 pathway, and *ATP2A2* (extracranial form), encoding a transporter that promotes aortic aneurysms. Notably, LCA grouped GCA clinical predisposition into four classes capturing cranial-predominant, mixed, extracranial, and ischemic/occlusive patterns, the latter representing a high-risk subgroup for severe ischemic and ocular complications.

Conclusions. This first genome-wide association study stratified by GCA-specific manifestations deepens our understanding of the genetic basis underlying GCA clinical heterogeneity. Our findings highlight HLA and non-HLA contributors to specific disease phenotypes and support the potential of genetic profiling to guide early diagnosis and personalized management in GCA.

Key words: Giant cell arteritis, genome-wide association study, patient stratification, single-nucleotide polymorphism, human leukocyte antigen region, latent class analysis.

KEY MESSAGES

What is already known on this topic

- Giant cell arteritis (GCA) is a clinically heterogeneous disease presenting a wide spectrum of cranial and large-vessel manifestations, posing challenges for timely diagnosis and optimal management.
- The genetic contribution to this clinical variability remains largely unknown and has not been systematically explored through large-scale genome-wide analyses.

What this study adds

- A stratified genome-wide associated study (GWAS) identified 14 risk loci associated with major GCA clinical manifestations, including seven mapping within the human leukocyte antigen (HLA) region and seven outside it.
- Functional annotation of these associated-loci enabled the prioritization of biologically relevant genes as the most likely candidates driving distinct GCA clinical features.
- Latent class analysis (LCA) based on the clinically-associated genetic variants identified four genetic classes with distinct GCA clinical patterns, including a subgroup at increased risk of ischaemic complications and vision loss, with potential implications for personalized management.

How this study might affect research, practice or policy

- The identification of genetic classes linked to distinct GCA clinical profiles represents a step towards genotype-informed stratification and may help guide future clinical decision-making in GCA.

INTRODUCTION

Giant cell arteritis (GCA) is the most common systemic vasculitis in adults over 50 years of age, characterized by granulomatous inflammation affecting large- and medium-sized arteries, particularly the aorta and its branches [1]. The clinical spectrum of GCA is highly heterogeneous, with patients presenting a wide range of manifestations. These include cranial symptoms, such as headache, vision abnormalities, and ischemic stroke, as well as extracranial manifestations, including polymyalgia rheumatica and limb claudication [2,3]. This clinical variability poses significant challenges for both diagnosis and management, especially in patients who present with ischemic symptoms, for whom early identification is crucial to prevent irreversible damage, emphasizing the need for improved diagnostic tools and personalized treatment approaches.

GCA is a complex disease influenced by both genetic and environmental factors. Recent genome-wide association studies (GWAS) have provided valuable insights into GCA susceptibility, identifying multiple risk loci, particularly within the human leukocyte antigen (HLA) region, mainly the classical allele DRB1*04, as well as genes involved in immune regulation (*CCDC25*), and vascular remodeling and angiogenesis (*PLG*, *P4HA2*, *MFGE8*, and *VTN*) [4,5]. Additionally, candidate gene association studies have highlighted the multifactorial nature of GCA clinical heterogeneity by identifying specific genetic associations with the presence of ischemic complications [6–8]. These findings suggest that genetic factors may contribute not only to disease susceptibility but also to diverse clinical presentations. However, while GWAS have significantly advanced our understanding of genetic susceptibility to GCA, large-scale studies specifically focused on the genetic determinants of its clinical complications remain lacking.

To address this gap, we leveraged the increased statistical power of the latest GWAS on GCA to perform a stratified analysis aimed at uncovering the genetic basis of clinical heterogeneity in this vasculitis. By categorizing patients based on specific clinical features, we identified genetic variants with a potential role as disease progression biomarkers. Furthermore, we applied latent class analysis (LCA) to link genetic variation with clinically relevant phenotypes, thus advancing our understanding of GCA pathogenesis and contributing to improve clinical stratification.

METHODS

Study population

Imputed genomic data from 3,498 patients with GCA and 15,550 healthy individuals of European ancestry from a previous GWAS [5] were re-analyzed in the present study according to specific clinical manifestations of the disease. This dataset comprised ten cohorts across France, Germany, Ireland, Italy, Norway, the Netherlands, Spain, Switzerland, the UK, and North America. Patients were diagnosed with GCA if they fulfilled the 1990 ACR classification criteria [9]. However, a diagnosis of GCA was also established if an imaging technique (temporal artery ultrasound, PET-CT, or MRI) yielded positive results, regardless of temporal artery biopsy findings.

Patients were stratified based on the following GCA-related manifestations: polymyalgia rheumatica (PMR); permanent visual loss (PVL); visual manifestations (VM), including transient visual loss, permanent visual loss, or diplopia; jaw claudication (JawC); limb claudication (LimbC); and age at disease onset (early onset: <65 years; non-early onset: ≥65 years). All clinical variables not collected for a given patient were treated as missing data.

Additionally, we considered two composite categories that group related ischemic and occlusive disease manifestations: irreversible occlusive disease (IOD), if patients had at least one of the following: PVL, stroke, or LimbC (excluding transient ischemic attacks, diplopia and transient visual loss); and severe ischemic manifestations (SIM), if they suffered at least one of the following complications: VM, cerebrovascular accidents (stroke and/or transient ischemic attacks), JawC, or LimbC.

Finally, patients were classified into cranial and extracranial subtypes of GCA. The cranial subtype included those patients presenting with headache, JawC, or VM (with or without PVL), regardless of the presence or absence of PMR. In contrast, the extracranial subtype comprised patients with limb claudication or PMR but without cranial ischemic manifestations of GCA.

Statistical analysis

Genotyping, quality control, imputation and principal component analysis (PCA) of each cohort were performed as previously described [5]. Briefly, standard filtering criteria were applied, and genotype imputation was performed using the TOPMed Imputation Server [10] with the TOPMed reference data as a reference panel. HLA imputation was performed using the SNP2HLA method [11] in conjunction with the Beagle software package and the Type 1 Diabetes Genetics Consortium as reference panel [12].

To maximize statistical power and ensure adequate case numbers within each subgroup, all cohorts were merged into a single combined dataset for the stratified analyses. Additional quality control procedures were then applied, including the exclusion of SNPs deviating from Hardy–Weinberg equilibrium ($p < 1\times10^{-5}$) and with a minor allele frequency <0.01. To account for potential population structure and batch effects, PCA was performed using approximately 100,000 independent SNPs to calculate ten PCs. Samples that deviated more than four standard deviations from the cluster centroids were considered outliers and excluded from further analyses.

After patient stratification, logistic regression analyses were performed on a total of 6,691,295 SNPs using PLINK [13], including sex and the first ten PCs as covariates. Three separate comparisons were performed for each clinical manifestation: i) patients with the manifestation versus unaffected controls (positive subphenotype comparison), ii) patients with the manifestation versus patients without the manifestation (intracase comparison), and iii) patients without the manifestation versus unaffected controls (negative subphenotype comparison). For each comparison, we calculated the genomic inflation factor (λ) and LDSC's intercept [14], to evaluate if the population stratification was correctly addressed in our study. Significant associations were also tested within each individual cohort and combined through meta-analysis to evaluate whether population stratification influenced the results.

A genetic signal was considered specifically associated with a clinical phenotype if it met the following criteria: it reached genome-wide significance (p-value $< 5\times10^{-8}$) in the positive subphenotype comparison, showed nominal evidence of association (p-value $< 1\times10^{-3}$) in the intracase comparison, and did not reach significance in the negative subphenotype comparison (p-value > 0.05) (or reached significance but with opposite effects compared to the positive subphenotype).

Post-hoc statistical power was calculated using the GAS Power Calculator, based on the observed minor allele frequency in controls, the reported odds ratio, the corresponding sample size, and a genome-wide significance threshold of $p<5\times10^{-8}$.

Additional methods

Details of additional tests to define manifestation-specific associations, HLA independence analysis, functional annotation of associated variants, latent class clustering model of patients, and external evaluation of the proposed genetic classes can be found in **Supplementary Materials.**

RESULTS

After quality control, a total of 3,470 patients with GCA, stratified according to nine GCA-related manifestations (PMR, VM, JawC, LimbC, PVL, age at onset, IOD, SIM, and cranial/extracranial phenotype), and 15,526 controls were included in the analysis. Details of the sample size of each considered clinical manifestation are shown in **Table 1** and **Supplementary Table 1**. To illustrate the clinical overlap within these manifestations, a Pearson correlation matrix has been added as **Supplementary Figure 1**. No prominent genomic inflation was observed in any of the comparisons (LDSC's intercepts < 1.06), after correcting for sex and the first ten PCs (**Supplementary Table 2)**.

Table 1. Sample size of the stratification of patients with giant cell arteritis for the considered clinical manifestations.

Clinical manifestation	N positive	N negative
Cranial phenotype	2950	198
Polymyalgia rheumatica	1338	1883
Visual manifestations	1141	1974
Permanent visual loss	562	2601
Jaw claudication	1484	1748
Limb claudication	290	2709
Severe ischemic manifestations*	2095	1026
Irreversible occlusive disease**	875	2050
Early disease onset (age < 65 y.o.)	581	2750

*Patients were considered to have severe ischemic manifestations if they suffered at least one of the following complications: visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or limb claudication.
**Patients were considered to have irreversible occlusive disease (excluding transient ischemic attacks, diplopia, and transient visual loss) if they had at least one of the following: permanent visual loss, stroke, or limb claudication.

HLA associations with specific clinical subphenotypes

Regarding the HLA region, associations with all the considered clinical manifestations, except LimbC, were identified after the imputation of classical alleles, amino acids, and SNPs (**Table 2, Supplementary Figures 2-9**). To ensure the robustness of the results, the lead HLA variants from the positive subphenotype comparisons were evaluated separately in each cohort and subsequently combined in a meta-analysis, revealing highly consistent effect estimates and low heterogeneity across cohorts (**Supplementary Table 3**).

Notably, the classical allele DQA1*0201 was associated with an increased risk for several subphenotypes, including patients with JawC ($p=4.04x10^{-12}$; OR [CI 95%]=1.43 [1.29-1.58]), those with a later onset of the disease ($p=4.39x10^{-12}$; OR [CI 95%]=1.33 [1.23-1.44]), and patients with the cranial phenotype of GCA ($p=6.77x10^{-11}$; OR [CI 95%]=1.32 [1.21-1.43]). In contrast, the classical allele DQB1*0602 was found to have an independent protective effect in patients with a later onset ($p=2.10x10^{-19}$; OR [CI 95%]=0.60 [0.54-0.67]) and in those with the cranial form of the disease ($p=9.58x10^{-20}$; OR [CI 95%]=0.60 [0.54-0.67]). Additionally, the SNPs rs5026743 was independently associated with the cranial phenotype ($p=2.72x10^{-61}$; OR [CI 95%]=0.58 [0.54-0.62]). The presence of histidine at amino acid position 96 of the DRB1 molecule was found to confer a protective effect specifically in patients with PMR. Moreover, three SNPs were associated with an increased risk of other specific clinical manifestations, including VM (rs204993: $p=1.42x10^{-10}$; OR [CI 95%]=1.36 [1.24-1.49]), PVL and IOD (rs9275602: $p=1.21x10^{-8}$; OR [CI 95%]=1.55 [1.33-1.80]; $p=1.59x10^{-10}$; OR [CI 95%]=1.50 [1.32-1.69], respectively), and SIM (rs3130286: $p=5.97x10^{-16}$; OR [CI 95%]=0.69 [0.63-0.75]). Interestingly, these SNPs were found to regulate gene expression levels of HLA genes and other immune-relevant genes, such as *C4A*, *C4B*, and *NOTCH4* (**Supplementary Table 4**). Pairwise linkage disequilibrium between all 7 lead HLA variants confirmed that they capture non-redundant haplotypic information (**Supplementary Table 5**).

Table 2. HLA genetic signals specifically associated with clinical manifestations of giant cell arteritis.

			Positive subphenotype comparison		Negative subphenotype comparison		Intracase comparison
HLA association	**Nearest gene**	**Phenotype**	**p**	**OR (CI 95%)**	**p**	**OR (CI 95%)**	**p**

		JawC	4.04×10^{-12}	1.43 (1.29-1.58)	6.96×10^{-2}	1.10 (0.99-1.21)	7.34×10^{-5}
DQA1*0201	*DQA1*	Late onset	4.39×10^{-12}	1.33 (1.23-1.44)	1.95×10^{-1}	0.89 (0.74-1.06)	1.76×10^{-5}
		Cranial	6.77×10^{-11}	1.32 (1.21-1.43)	2.61×10^{-3}	0.57 (0.40-0.82)	5.12×10^{-6}
		Late onset	2.10×10^{-19}	0.60 (0.54-0.67)	5.58×10^{-2}	0.83 (0.69-1.01)	2.72×10^{-3}
DQB1*0602	*DQB1*						
		Cranial	9.58×10^{-20}	0.60 (0.54-0.67)	4.95×10^{-1}	1.11 (0.82-1.51)	4.31×10^{-4}
rs5026743	*DRA*	Cranial	2.72×10^{-61}	0.58 (0.54-0.62)	6.17×10^{-2}	0.82 (0.67-1.01)	2.96×10^{-3}
		PVL	1.21×10^{-8}	1.55 (1.33-1.80)	4.97×10^{-1}	1.03 (0.95-1.12)	1.63×10^{-6}
rs9275602	*DQA2*						
		IOD	1.59×10^{-10}	1.50 (1.32-1.69)	5.21×10^{-1}	0.97 (0.88-1.07)	1.17×10^{-8}
DRB1-96-His	*DRB1*	PMR	7.15×10^{-15}	0.72 (0.67-0.78)	5.00×10^{-2}	0.93 (0.87-1.00)	7.34×10^{-8}
rs204993	*PBX2*	VM	1.42×10^{-10}	1.36 (1.24-1.49)	6.33×10^{-2}	1.08 (1.00-1.16)	1.43×10^{-4}
rs3130286	*CYP21A2*	SIM	5.97×10^{-16}	0.69 (0.63-0.75)	1.02×10^{-1}	0.91 (0.81-1.02)	6.98×10^{-5}

JawC, jaw claudication; PVL, permanent vision loss; IOD, irreversible occlusive disease; PMR, polymyalgia rheumatica; VM, visual manifestations; SIM, severe ischemic manifestations; OR, odds ratio; CI, confidence interval.

Non-HLA associations with specific clinical subphenotypes

Outside the HLA region, logistic regression analyses identified seven genetic variants significantly associated with an increased risk of developing specific clinical manifestations across all considered clinical phenotypes, except for PVL and age at onset (**Figure 1, Table 3, Supplementary Figures 10-16**). These susceptibility loci included: *CAMKMT* (2p21), associated with the PMR subphenotype ($p=4.01 \times 10^{-8}$; OR [CI 95%]=2.01 [1.57-2.58]); *ATP6V1E2* (2p21), conferring risk for VM development ($p=4.14 \times 10^{-8}$; OR [CI 95%]=3.19 [2.11-4.83]); *ELOA* (1p36.11), associated with JawC presence ($p=1.36 \times 10^{-8}$; OR [CI 95%]=3.13 [2.11-4.64]); *ADAMTS9* (3p14.1) and *IL17A* (6p12.2), both associated with LimbC development ($p=1.44 \times 10^{-8}$; OR [CI 95%]=5.82 (3.17-10.70); $p=2.03 \times 10^{-8}$; OR [CI 95%]=2.46 [1.80-3.37], respectively); *PLG* (6q26), conferring risk for SIM ($p=1.62 \times 10^{-15}$; OR [CI 95%]=1.33 [1.24-1.42]); and *CCDC63* (12q24.11) associated with the extracranial form of the disease ($p=1.12 \times 10^{-8}$; OR [CI 95%]=5.45 [3.05-9.75]).

The lead SNPs for each positive-subphenotype comparison were examined separately in each cohort and subsequently meta-analyzed, confirming consistent effect directions across cohorts (**Supplementary Table 6**).

Table 3. Non-HLA genetic signals specifically associated with clinical manifestations of giant cell arteritis.

					Positive subphenotype comparison		Negative subphenotype comparison		Intracase comparison
Clinical manifestation	**Region**	**SNP**	**EA**	**Nearest gene**	**p**	**OR (CI 95%)**	**p**	**OR (CI 95%)**	**p**
JawC	1p36.11	rs72663289	C	*ELOA*	$1.36x10^{-8}$	3.13 (2.11-4.64)	$9.42x10^{-1}$	0.98 (0.55-1.75)	$4.06x10^{-4}$
PMR	2p21	rs116098507	A	*CAMKMT*	$4.01x10^{-8}$	2.01 (1.57-2.58)	$4.30x10^{-1}$	0.88 (0.65-1.20)	$3.01x10^{-5}$
VM	2p21	rs6746695	G	*ATP6V1E2*	$4.14x10^{-8}$	3.19 (2.11-4.83)	$7.44x10^{-1}$	1.08 (0.68-1.70)	$2.65x10^{-4}$
LimbC	3p14.1	rs79433524	G	*ADAMTS9*	$1.44x10^{-8}$	5.82 (3.17-10.70)	$2.56x10^{-1}$	1.26 (0.84-1.89)	$2.15x10^{-5}$
	6p12.2	rs73437731	C	*IL17A*	$2.03x10^{-8}$	2.46 (1.80-3.37)	$3.52x10^{-1}$	1.08 (0.91-1.29)	$1.15x10^{-6}$
SIM	6q26	rs9458017	T	*PLG*	$1.62x10^{-15}$	1.33 (1.24-1.42)	$8.03x10^{-2}$	1.09 (0.99-1.20)	$2.27x10^{-4}$
Extracranial	12q24.11	rs61944267	C	*CCDC63*	$1.12x10^{-8}$	5.45 (3.05-9.75)	$3.78x10^{-1}$	0.88 (0.66-1.17)	$5.19x10^{-7}$

JawC, jaw claudication; PMR, polymyalgia rheumatica; VM, visual manifestations; LimbC, limb claudication; SIM, severe ischemic manifestations; SNP, single-nucleotide polymorphism; EA, effect allele; OR, odds ratio; CI, confidence interval.

For all identified signals, subset-based meta-analysis confirmed that only the positive subphenotype subset contributed significantly to the associations (**Supplementary Table 7**). Additionally, meta-analysis of effect sizes from the positive and negative subphenotype comparisons revealed significant heterogeneity (**Supplementary Table 8**), supporting that the identified associations are subphenotype-specific.

Functional annotation of non-HLA signals

Since none of the lead non-HLA SNPs were located within coding regions, we performed a comprehensive functional annotation to explore their potential regulatory roles and prioritize the most likely causal genes.

According to functional annotation results, three lead SNPs were identified as eQTLs in whole blood (**Figure 2** and **Supplementary Table 9**). Specifically, the G allele of rs6746695, which was associated with the development of VM, appeared to downregulate the expression of *ATP6V1E2*, while upregulating *CRIPT.* The C allele of rs73437731, associated with the presence of LimbC, was linked to increased expression levels of *PAQR8*. Finally, the C allele of rs61944267, a variant associated with the extracranial phenotype, was found to increase the expression of *ATP2A2* and to decrease the expression of *GPN3* and *ARPC3.* In addition to its role as an eQTL, this variant also acted as a sQTL, influencing the splicing of *GPN3*.

Beyond these regulatory effects, other genes located within the associated loci were prioritized based on their genomic proximity to the lead SNPs and biological relevance to GCA, including previously implicated immune and vascular genes (**Figure 2**). Altogether, this integrative annotation strategy supported the prioritization of 17 genes as potential mediators of the genetic associations identified in this study.

Post-hoc power calculations for all lead associations are provided in **Supplementary Table 10**; while power was adequate for the majority of signals, statistical power was limited for associations identified in smaller subphenotype subgroups.

Four latent genetic classes in GCA

LCA indicated that patients with GCA were best stratified into four classes based on genetic profiles; adding a fifth class yielded only a minimal decrease in BIC (**Figure 3a**). Robustness metrics supported this solution: entropy was 0.929 (range 0–1; >0.80 indicates strong and reliable separation), and the mean maximum posterior probability was 0.968, reflecting high certainty in individual class assignments (**Figure 3b**). Consistently, 91.2% of individuals had a class membership probability ≥90%, indicating low overall assignment uncertainty.

To confirm that the four-class model provided the optimal stratification, we compared it against three- and five-class solutions (**Supplementary Table 11**). Although the five-class model showed a marginal improvement in BIC, it did not improve classification certainty. In contrast, the four-class model demonstrated the highest entropy, the highest mean maximum posterior probability, and the largest number of patients with class assignment probabilities exceeding 90%. Taken together, these metrics indicated that the four-class model offered the most reliable classification of the cohort.

Evaluation of the use of the variables in the classification (**Supplementary Figure 17**) shows that the most prominent difference in class assignments is attributable to differences in HLA variants. Patients presenting HLA-DQA1*0201 and rs5026743-TT are most frequently categorized in class 1, those presenting HLA-DQB1*0602 and rs5026743-GT were mostly classified as class 3; and class 4 was characterized by the presence of rs9275602-A and rs204993-CT. Other variants exhibited more gradual or only minor differences across classes. Class 2 did not show overrepresentation of any particularly characteristic risk variants, suggesting that genetics (as captured by these variants) does not delineate this class strongly.

GCA genetic classes show distinct clinical profiles

Analysis of GCA genetic classes revealed significant differences in clinical manifestations across groups (**Figure 3c**; statistical details in **Supplementary Table 12**). Class 1 (n = 853) exhibited a predominantly cranial pattern: JawC, headache, and SIM were more frequent (RR = 1.22 [1.13–1.32]; RR = 1.10 [1.07–1.14]; and RR = 1.08 [1.02–1.14], respectively). In contrast, extracranial features were less common, with reduced PMR (RR = 0.86 [0.78–0.96]) and a notably lower prevalence of LimbC (RR = 0.55 [0.40–0.75]). Despite the cranial-leaning profile, visual loss was also less frequent in this class (RR = 0.76 [0.63–0.92]). Class 2 (n = 1,292) displayed marked clinical heterogeneity combining clinical features of both cranial and large-vessel forms of GCA without a prominent defining feature. Compared with the other classes, this group showed slightly lower frequencies of headache (RR = 0.94 [0.91-0.97]) and JawC (RR = 0.86 [0.80-0.93]) while other manifestations such as PVL, stroke, LimbC, and PMR were also represented, although without statistically significant differences compared with the other classes. Class 3 (n = 516) exhibited a comparatively extracranial profile. Notably, this group showed a markedly reduced risk of visual complications, including VM (RR = 0.73 [0.63-0.85]) and PVL (RR = 0.58 [0.44-0.76]). Similarly, JawC and SIM were also less frequent in this group. In contrast, PMR and LimbC tended to be more common, although these differences did not reach statistical significance. Class 4 (n = 809), on the other hand, showed a distinct profile with a higher risk of severe ischemic complications of GCA, including SIM (RR = 1.10 [1.04-1.16]), IOD (RR = 1.35 [1.20-1.52]) and vision-related complications: VM (RR = 1.31 [1.18-1.44]) and PVL (RR = 1.45 [1.23-1.70]) In contrast, milder manifestations did not significantly deviate from the cohort average.

Cranial and extracranial GCA subtypes were correlated with the classes, as cranial GCA were significantly more present in class 1 (RR = 1.05 [1.04-1.07]), while extracranial GCA was significantly more prevalent in class 2 (RR = 1.02 [1.00-1.04]) and class 3 (RR = 1.04 [1.01-1.08]).

Evaluation of the GCA clustering model in an independent cohort

After quality controls, 1,043 patients with GCA were included as an independent cohort to assess the reproducibility of the four-class model. Overall, the prevalence of clinical manifestations was lower than in the discovery cohort, with the exception of stroke (**Supplementary Table 13**). Following application of the LCA model, 82.9% of

individuals presented a predominant genetic class with a probability ≥90%（**Figure 4A**). Consistently, the mean maximum posterior probability was 94.1%, indicating a high level of confidence in class assignment. Comparison of class-specific clinical patterns between cohorts (**Figure 4B**; **Supplementary Table 14**; **Supplementary Figure 18**) showed a strong correlation for class 1 (r=0.75), consistently reproducing the clinical patterns observed in the discovery cohort, and a modest correlation for class 4 (r=0.50). Although the replication of its general clinical profile was moderate, class 4 showed a trend towards increased risk of permanent visual loss (RR = 1.53 [0.84-2.80]) and irreversible occlusive disease (RR = 1.20 [0.87-1.65]), similar to the predominant ischaemic pattern observed in the discovery cohort. Finally, classes 2 and 3 displayed weak correlations (r=0.28 and r=0.32, respectively) between cohorts.

DISCUSSION

This study represents the first large-scale analysis of the genetic architecture underlying clinical manifestations in GCA. Our results provide novel insights into its clinical heterogeneity and suggest potential applications of these genetic findings for patient stratification. With the exception of the *PLG* locus, none of the identified associations had been reported in the previous non-stratified GCA GWAS [5], suggesting that stratification by clinical manifestation reveals genetic signals that would otherwise remain undetected.

Consistent with previous studies, our findings reinforce the central role of the HLA region in the genetic architecture of GCA, but also expand this knowledge by demonstrating that specific variants within this locus can influence the clinical heterogeneity of the disease. The risk conferred by DQA1*0201 across subphenotypes, coupled with the strong protective effect of DQB1*0602 and the association of histidine at amino acid position 96 of DRB1 in PMR patients, supports a role for HLA class II-mediated antigen presentation in shaping the clinical expression of GCA. Furthermore, the identification of independent SNP associations within the HLA locus indicates that regulatory variants may also contribute to subphenotype-specific risk.

Outside the HLA region, seven additional signals were associated with specific clinical features. Functional annotation of these signals showed that some of the identified genetic variants may exert regulatory effects by modulating gene expression, while others were located near genes with functions closely related to GCA pathophysiology. These findings enable us to prioritize certain genes (*IL22RA1*, *IL17A/IL17F*, *ADAMTS9*,

CAMKMT, *ATP2A2*, and *PLG/LPA*) as the most likely candidates to be involved in the development of this vasculitis.

Several of the prioritized genes, *IL22RA1*, *IL17A* and *IL17F*, are key effectors of the Th17 pathway [15], a central driver of GCA pathogenesis [16]. *IL22RA1*, which maps to the genomic locus associated with the JawC phenotype, encodes a subunit of the receptor for IL-22, which is expressed on stromal cells and may mediate immune–tissue crosstalk [17,18]. It has been reported that both IL-22 and its receptor IL-22R1 are expressed at higher levels in inflamed temporal artery biopsies from GCA patients [19]. Interestingly, patients with biopsy-proven GCA also exhibited increased plasma levels of IL-22 compared with biopsy-negative patients [18]. Since positive temporal artery biopsies are more frequently observed in patients with cranial manifestations, this finding may suggest a preferential involvement of IL-22 in cranial forms of the disease, a hypothesis supported by our current results, which show a specific genetic association between *IL22RA1* and the development of JawC.

Notably, while *IL22RA1* was associated with a cranial symptom, *IL17A* and *IL17F*, also encoding pro-inflammatory cytokines of the Th17 axis, were specifically associated with the extracranial manifestation LimbC. Among them, IL-17A is the most extensively studied in GCA and has been consistently involved in its pathogenesis. In this regard, massive infiltration of IL-17–positive T lymphocytes together with increased levels of IL-17A have been reported in inflamed temporal arteries and plasma from patients with GCA [20,21].

Different drugs targeting the IL-17 pathway, such as secukinumab and ixekizumab, are approved for the treatment of several autoimmune diseases, including psoriasis, psoriatic arthritis, and ankylosing spondylitis [22]. More recently, IL-17A blockade has been shown to be effective in preliminary studies involving GCA patients, suggesting a potential therapeutic role in this vasculitis [23]. Our genetic finding that *IL17A* is specifically associated with LimbC provides further support for this therapeutic strategy and suggests that IL-17A inhibitors could be particularly beneficial in patients with predominant extracranial symptoms, thus helping to guide personalized treatment approaches.

Another association related to the development of LimbC mapped to the *ADAMTS9* gene. This gene encodes a member of the ADAMTS family, an extracellular matrix-degrading enzyme involved in key processes such as vascular smooth muscle cell proliferation and migration, as well as inhibition of angiogenesis [24].

CAMKMT was the only gene prioritized at the locus associated with PMR. Although this gene had not previously been directly linked to GCA, it encodes a methyltransferase that post-translationally modifies several calmodulin-dependent protein kinases that play well-established roles in inflammatory signaling and vascular responses [25]. Moreover, their activity depends on calcium-bound calmodulin, which itself regulates pro-inflammatory pathways [26–28].

Expression levels of three genes, *ATP2A2*, *GPN3* and *ARPC3*, were affected by the genetic variant specifically associated with the extracranial subphenotype. Interestingly, it has been reported that the inactivation of SERCA2, an endoplasmic reticulum ATPase Ca(2+) transporter encoded by *ATP2A2*, promotes the development of aortic aneurysms, one of the major extracranial complications of GCA [29,30].

Finally, our findings show that the signal at 6q26, an established susceptibility locus in GCA [4,5], is specifically associated with the development of SIM. Two genes involved in the plasminogen pathway were prioritized at this locus: *PLG*, encoding plasminogen, and *LPA*, encoding a serine proteinase that inhibits the activity of tissue-type plasminogen activator (tPA). Notably, both genes have been implicated in ischemic processes [31,32]. Indeed, plasminogen activation via tPA is a key therapeutic approach in acute ischemic stroke, highlighting the relevance of this pathway. These observations support a potential role for *PLG* and *LPA* in the risk of developing SIM in GCA patients.

A refined disease stratification for GCA is clinically imperative, as the current one-size-fits-all approach to GCA management leads to both overuse of glucocorticoids and preventable complications such as permanent ocular damage; more precise classification would enable individualized therapy and early identification of high-risk phenotypes [33]. To integrate the genetic biomarkers associated with specific GCA manifestations into a clinically meaningful framework that could improve GCA management, we applied LCA based solely on the significant variants identified. This unsupervised approach has provided new insights into other heterogeneous inflammatory conditions, like undifferentiated arthritis [34], coeliac disease [35], and spondyloarthritis [36]. In our study, LCA identified four genetic classes with partially distinct clinical profiles: cranial-predominant (Class 1), mixed-pattern (Class 2), extracranial (Class 3), and ischemic/occlusive (Class 4) GCA.

Of particular relevance, class 4 was characterized by an enrichment of severe ischemic and ocular manifestations. The early identification of patients with a markedly higher risk of severe visual manifestations, which are not necessarily preceded by milder symptoms,

suggests a potential avenue for risk stratification, although prospective studies are needed to determine whether genotype-informed approaches can translate into earlier therapeutic intervention and prevention of visual loss. This model is consistent with observations that ischemic ocular symptoms in GCA may develop independently of prominent cranial involvement [37].

Class 1 displayed a clear cranial pattern of GCA, with higher frequencies of headache, jaw claudication, and ischaemic manifestations. This profile supports a stratified diagnostic approach, in which patients in this class could be preferentially assessed using temporal artery biopsy, given the predominance of cranial involvement, while patients from other classes could be more appropriately evaluated using alternative imaging modalities, in order to avoid unnecessary invasive procedures. Interestingly, despite the greater cranial involvement, this class did not show an increased frequency of visual complications, which raises the possibility that glucocorticoid dose and duration could potentially be tailored in this subgroup, pending confirmation in longitudinal studies.

Evaluation of this stratification strategy in the UK Biobank showed that genetic classes could be robustly assigned in an independent cohort, with partial replication of the clinical patterns, particularly for classes 1 and 4. Interpretation of these clinical profiles should, however, be considered in light of several limitations. The lower prevalence of GCA-related manifestations in the UK Biobank cohort, as well as its inferior sample size, likely reduced the power to detect consistent patterns between datasets. In addition, the use of ICD-10 codes may incompletely capture specific GCA features, and the healthier profile of UK Biobank participants, who are known to have lower disease burden and fewer severe clinical outcomes than the general population [38], may have led to an underrepresentation of clinical manifestations, thereby biasing comparisons between cohorts. Overall, these findings should be interpreted as a proof-of-concept evaluation of the proposed stratification strategy rather than a definitive external replication.

A limitation of the present study relates to statistical power in stratified analyses of specific GCA manifestations. Although the overall sample size is large for a vasculitis study, several clinical subphenotypes remain relatively infrequent. Consequently, even after combining multiple independent cohorts into a single dataset to improve power, some subgroup analyses remained limited by low case numbers, which may lead to inflated effect size estimates, particularly for rarer manifestations. In addition, differences in allele frequencies and linkage disequilibrium patterns across European populations could contribute to spurious associations. As a result, some of the reported associations

should be considered hypothesis-generating and will require further replication in independent cohorts.

Together, the findings of this research indicate that integrating genetic stratification into clinical practice could refine current subtyping of GCA and provide a basis for more individualized patient monitoring and prognostic assessment.

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Data availability statement. Summary statistics from all stratified analyses in this study are publicly accessible through Zenodo (repository will be made live upon manuscript acceptance).

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FIGURE LEGENDS

Figure 1. Circular Manhattan plots of genetic associations with clinical manifestations of giant cell arteritis. The angular axis represents genomic position by chromosome, and the radial axis shows the $-\log_{10}$(p-value) of each analysed SNP. The dotted circular line marks the genome-wide significance threshold ($p < 5x10^{-8}$). SNPs meeting all established criteria for genome-wide significance are highlighted in colour: blue for non-HLA associations and red for HLA associations. The nearest gene to each significant signal is indicated.

Figure 2. Functional annotation and gene prioritization of SNPs associated with distinct GCA clinical manifestations. For each locus, only the top prioritized genes are displayed. The colours indicate the SNPs that overlap with the considered functional annotations for each specific gene. Different colours indicate different categories of annotations, including the genomic location of the genetic variants (orange), their correlation with gene expression (blue) and splicing changes (purple), evidence of chromatin interaction (green), and potential candidate genes based on literature (red). SNP, single-nucleotide polymorphism; eQTL, expression quantitative trait loci; sQTL, splicing quantitative trait loci.

Figure 3. Performance and clinical profiling of the latent class model. (A) Model selection based on BIC identifying the optimal number of classes. (B) Class assignment certainty across individuals for their predominant class. (C) Distribution of clinical manifestations by class, shown as deviation from the cohort mean prevalence. * Significant correlation (FDR-adjusted $p < 0.05$).

Figure 4. Evaluation of the 4-class model using UKBB data. (A) Certainty in class assignment (as posterior probability of the predominant class) for the UKBB cohort, after applying the established latent class clustering model. (B) Correlation of class-specific risk estimates for clinical manifestations between cohorts.