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Vasculitis

Age, anticoagulants, hypertension and cardiovascular genetic traits predict cranial ischaemic complications in patients with giant cell arteritis

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ABSTRACT

Objectives: This project aimed to determine whether cranial ischaemic complications at the presentation of giant cell arteritis (GCA) were associated with pre-existing cardiovascular (CV) risk factors, CV disease or genetic risk of CV-related traits.

Methods: 1946 GCA patients with clinicodemographic data at GCA presentation were included. Associations between pre-existing CV-related traits (including Polygenic Risk Scores (PRS) for CV traits) and cranial ischaemic complications were tested. A model for cranial ischaemic complications was optimised using an elastic net approach. Positional gene mapping of associated PRS was performed to improve biological understanding.

Results: In a sample of 1946 GCA patients (median age = 71, 68.7% female), 17% had cranial ischaemic complications at presentation. In univariable analyses, 10 variables were associated with complications (likelihood-ratio test $p \leq 0.05$). In multivariable analysis, the two variables with the strongest effects, with or without PRS in the model, were anticoagulant therapy (adjusted OR (95% CI) = 0.21 (0.05 to 0.62), $p = 4.95 \times 10^{-3}$) and age (adjusted OR (95% CI) = 1.60 (0.73 to 3.66), $p = 2.52 \times 10^{-3}$, for ≥80 years versus <60 years). In sensitivity analyses omitting anticoagulant therapy from multivariable analysis, age and hypertension were associated with cranial ischaemic complications at presentation (hypertension: adjusted OR (95% CI) = 1.35 (1.03 to 1.75), p = 0.03). Positional gene mapping of an associated transient ischaemic attack PRS identified *TEK*, *CD96* and *MROH9* loci.

Conclusion: Age and hypertension were risk factors for cranial ischaemic complications at GCA presentation, but in this dataset, anticoagulation appeared protective. Positional gene mapping suggested a role for immune and coagulation-related pathways in the pathogenesis of complications. Further studies are needed before implementation in clinical practice.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Age and cardiovascular risk factors have been suggested as risk factors for cranial ischaemic complications of giant cell arteritis (GCA), such as visual loss or stroke.

WHAT THIS STUDY ADDS

- This study confirms that age and prior hypertension are associated with cranial ischaemic complications of GCA. Anticoagulant therapy appears to be protective; this is a novel finding. Interrogation of an associated transient ischaemic attack polygenic risk score also revealed a genetic basis of risk through influence on immune and coagulation pathways.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This finding indicates the need for further evaluation of therapies that target thrombosis pathways in GCA, ultimately requiring testing in randomised controlled trials.

INTRODUCTION

Giant cell arteritis (GCA) is the most common primary systemic vasculitis affecting older people and without prompt treatment may result in irreversible visual loss [1]. Patients with GCA may present with systemic symptoms, such as fever, malaise and weight loss; cranial symptoms, such as headache, scalp tenderness, jaw or tongue claudication, with or without cranial ischaemic complications such as vision loss or stroke; symptoms relating to large-vessel involvement, such as limb claudication or critical limb ischaemia; or symptoms of polymyalgia rheumatica (proximal limb-girdle pain and stiffness). GCA is diagnosed following an assessment of these symptoms, clinical signs, laboratory markers of inflammation, temporal artery biopsy (TAB) and/or imaging of relevant vascular territories [2]. High-dose glucocorticoid therapy must be initiated promptly; higher doses are recommended for those with ischaemic complications. On subsequent tapering of glucocorticoids, relapse occurs in about half of all patients with GCA. Relapse is treated with high-dose glucocorticoids if there are ischaemic manifestations and by smaller dose escalations otherwise, along with glucocorticoid-sparing therapies [2,3].

A history of ischaemic manifestations at GCA diagnosis is linked with risk of subsequent visual loss [4]. We reasoned that identification of risk factors for ischaemic manifestations at GCA presentation might identify a subset of patients who may benefit from more intensive monitoring and potentially adjunctive treatments.

Various prior studies suggested that cranial ischaemic complications in GCA are associated with age [5] and prior cardiovascular (CV) risk factors, including atherosclerosis [6], stroke, peripheral vascular disease [7], hypertension [6] and socioeconomic status [8]. Ischaemic complications are less common in those with high levels of acute phase markers, erythrocyte sedimentation rate and C reactive protein [9]. Data are conflicting on whether antiplatelet/anticoagulant therapy may protect against ischaemic complications in GCA [10–13]. However, all these studies have been relatively small (less than 500 cases).

Larger population studies have demonstrated an excess risk of CV disease (CVD), hypertension and diabetes following a diagnosis of GCA [14–16], where dose-dependent associations have been demonstrated with glucocorticoid use [17]. However, vascular inflammation is also proatherogenic and disentangling the effects of age, lifestyle influences and medication from CV-related risk factors can be challenging. One approach to this is to examine ischaemic complications at presentation and the relationship between genetic predisposition to CV risk factors, using a Polygenic Risk Score (PRS) approach. A PRS estimates an individual's genetic propensity to a trait by enumerating the number of risk alleles they carry across multiple loci, weighted by the effect sizes of each estimated from a genome-wide association study (GWAS) [18]. Testing for such associations could provide evidence for the role of pre-existing or predisposed CV risk factors and ischaemic manifestations of GCA and could identify novel pathogenic mechanisms underlying both disorders.

Previous candidate gene studies have identified strong associations between GCA susceptibility and genes of the major histocompatibility complex (MHC) [19,20], as well as associations in genes related to vascular function [21] and cytokines [22]. A GWAS identified associations of GCA susceptibility with *HLA-DRB1* and *HLA-DQA1* in the HLA class II, *HLA-B* in the HLA class I, as well as loci in the region of *PLG* and *P4HA2* [23].

In this study, we aimed to identify associations between pre-existing CV risk factors, CVD or genetic risk of CV-related traits and cranial ischaemic complications at GCA presentation. We then constructed PRS for CV-related risk factors, tested these for association with ischaemic complications and evaluated the performance of these PRS alongside non-genetic risk factors. Finally, we used positional gene mapping to highlight the pathogenic mechanisms underlying PRS loci.

METHODS

Data source/study population

This study used individual-level clinicodemographic and genetic data from the UKGCA Consortium and UK Biobank. For details of both cohorts, and information about the genotyping, quality control and imputation of UKGCA genetic data, see online supplemental methods.

Study outcomes

The primary outcome was cranial ischaemic complications at presentation of GCA, including ocular and non-ocular complications. Secondary outcomes were a transient cranial ischaemic features composite (including ocular and non-ocular ischaemic features) and a composite of extracranial ischaemic manifestations, comprising extracranial ischaemic features (arm and leg claudication secondary to GCA) and/or extracranial ischaemic complications (fixed vascular stenosis to a limb secondary to GCA). For further details of outcome definitions, see online supplemental methods, table 1.

Patients with both cranial ischaemic complications and transient cranial ischaemic features recorded were retained in the primary cohort and removed from both the case and reference cohorts of the secondary (transient) outcome, in order to ensure mutual exclusivity. Individuals with both cranial ischaemic complications and extracranial ischaemic manifestations were not removed from the secondary (extracranial) outcome cohort, to prevent substantial losses in sample size (N = 203 with both outcomes vs N = 59 with solely secondary outcome).

Risk factors studied were pre-existing CVDs, CV risk factors, CV medication and CV-related trait PRS. Definitions of these risk factors may be found in online supplemental methods.

Using PRSice V.2.3.3 [24], PRSs were calculated for CVDs and CV risk factors using effect sizes from publicly available GWAS summary statistics or GWAS performed in white European UK Biobank data using linear or logistic regression in PLINK V.1.9 [25]. More details of this approach, as well as a full list of traits for which PRSs were calculated and their respective data sources, may be found in online supplemental methods, table 2.

Statistical analyses

We first described the clinical and sociodemographic characteristics of the UKGCA Consortium sample, including different classification/diagnostic criteria and subcohorts with ischaemic complications, and/or transient ischaemic features. Data were described with either number (N) and percentage (%), or median (MD) and lower IQR and upper IQR (Q1−Q3), unless otherwise stated.

Correlations between investigated risk factors were assessed using the Pearson correlation coefficient, R^2. One variable from any pair with $R^2 \geq 0.8$ was removed from further analyses.

Statistical analyses were performed in R V.3.6.2 to model the risk of cranial ischaemic complications in GCA using logistic regression. To reduce the number of df in our models, all non-binary risk factors (including PRS) were modelled as continuous variables.

Univariable analyses were first performed to test for associations between cranial ischaemic complications in GCA and clinical and sociodemographic variables.

Sensitivity analyses were then performed, removing individuals with either of the secondary outcomes (transient cranial ischaemic features or extracranial ischaemic manifestations) from the primary reference cohort, and re-evaluating univariable associations with cranial ischaemic complications.

Traits with a likelihood ratio (LR) test $p \leq 0.1$ in univariable regression were added to an elastic net regression model ($\alpha = 0.50$; $\lambda = 6.43 \times 10^{-3}$) to perform variable selection and reduce the number of redundant variables. Every variable was missing in some samples so the LR test p value threshold was chosen both to avoid possible bias by imputing these and to minimise sample loss in the elastic net regression. Variables retained using this technique were included in a complete-case multivariable logistic regression to assess effect sizes of risk factors.

Univariable associations between PRS and the primary outcome were tested; those PRS with LR test $p \leq 0.1$ were added to the clinical and sociodemographic model optimised using elastic net and logistic regression, in order to avoid substantial data losses due to the complete case approach used in subsequent analyses. Elastic net regression was used for variable selection, and effect estimates for the final clinical, sociodemographic and genetic model were retrieved with multivariate regression.

Finally, the resulting model was tested for association with the secondary outcomes (transient cranial ischaemic features and extracranial ischaemic manifestations) in logistic regression.

Trait PRS with an LR test $p \leq 0.05$ in univariable regression were further interrogated by positional mapping of genetic loci within the PRS. Genetic loci within 10 kb of a gene, or with known functional consequences (including exonic, splicing, intronic, 3'untranslated region (UTR) and 5' UTR single nucleotide polymorphisms (SNPs)) were mapped using Ensembl build 85 (V.11) [26] and ANNOVAR [27]. Furthermore, StringDB [28] network analysis was performed using proteins encoded by positionally mapped genes, and compared with proteins mapped by previous work [23,29].

Patient and public involvement

Patients and the public were not involved in the original design of the UKGCA Consortium, which commenced in 2005. However, the study has subsequently been discussed with patients with lived experience with GCA through the MRC TARGET Programme Management Board that includes three patient partners.

RESULTS

A total of 1946 UKGCA Consortium patients (94.8% (N = 1844/1946) with genetic data) were included in the analyses. The sample size for each of the analyses presented is provided to highlight missing clinical data. 99.2% (N = 1863/1878) were 'white European' (online supplemental methods) and 68.7% (N = 1331/1938) were female (table 1). The median age at diagnosis was 71 (IQR = 66−77) years. 93.0% (N = 1324/1424) fulfilled the 1990 American College of Rheumatology (ACR) classification criteria for GCA after imputation of ESR using CRP where necessary and 94.9% (N = 1583/1669) fulfilled 2022 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for GCA (see online supplemental methods). 69.2% (N = 992/1434) had a diagnosis of GCA confirmed by TAB and/or diagnostic vascular imaging (online supplemental table 3). No notable differences in demographic variables were observed between the overall cohort and any diagnostic category (table 1, online supplemental table 3), although a disproportionately high number of individuals (28.9%; 389/1346) fell within the UK population's 'least deprived' index of multiple deprivation 2019 quintile (online supplemental results).

Of 1946 UKGCA individuals in this study, 17.0% (N = 327/1925) had cranial ischaemic complications, 59.3% (N = 951/1604) had transient cranial ischaemic features, and 12.5% (N = 203/1630) had extracranial ischaemic manifestations (table 2). No differences in the prevalence of ischaemic manifestations were observed between the different diagnostic groups (online supplemental results, table 4) and subsequent analyses were performed on the total GCA cohort.

Of the cohort with cranial ischaemic complications (primary outcome), 15.6% (N = 43/275) also had symptoms suggestive of extracranial ischaemic features, and 2.2% (N = 6/300) had extracranial ischaemic complications (table 3). 26.9% (N = 80/298) of the cohort with cranial ischaemic complications reported PMR symptoms, with 63.8% of these (N = 51/80) reporting an onset of PMR symptoms before their GCA symptoms began. Further descriptions of cohorts in this work are summarised in online supplemental results, table 4–9.

Prior to the testing of univariable associations with the primary outcome, pairwise Pearson correlations were estimated between variables. No trait pairs were found to be strongly correlated (Pearson $R^2 \geq 0.80$) and all were retained in the analyses. A few traits had a correlation $R^2 \geq 0.45$, including hyperlipidaemia and cholesterol-lowering medication ($R^2 = 0.50$, $p = 3.44 \times 10^{-80}$), and atrial fibrillation (AF) and anticoagulant therapy ($R^2 = 0.49$, $p = 4.75 \times 10^{-66}$). More details of these correlations may be found in online supplemental table 10.

In univariable analyses, risk factors with associations with cranial ischaemic complications in GCA with an LR test $p < 0.05$ (table 4, online supplemental results, tables 11–13) included:

Table 1

Patient demographics at presentation: total GCA cohort; those fulfilling imputed 1990 ACR classification criteria; confirmed diagnosis by temporal artery biopsy or vascular imaging

	Total cohort (N = 1946)	Fulfilling imputed 1990 ACR classification criteria (N* = 1324/1424)	Diagnosis confirmed by biopsy/imaging (N* = 992/1434)
Age at diagnosis (years), median (IQR)	71 (66–77)	71 (66–77)	73 (68–78)
Female sex	1331/1938 (68.7%)	892/1320 (67.6%)	663/992 (66.8%)
Ethnicity			
EUR	1863/1878 (99.2%)	1273/1287 (98.9%)	954/963 (99.1%)
AFR	2/1878 (0.1%)	2/1287 (0.2%)	1/963 (0.1%)
SAS	13/1878 (0.7%)	12/1287 (0.9%)	8/963 (0.8%)
EAS	0/1878 (0%)	0/1287 (0%)	0/963 (0%)
Family history of GCA	26/947 (2.8%)	21/758 (2.8%)	11/448 (2.5%)
Family history of PMR	42/939 (4.5%)	34/751 (4.5%)	18/444 (4.1%)
BMI (kg/m^2)			
<18.5	21/937 (2.2%)	15/756 (2.0%)	13/454 (2.9%)
18.5 to <25	383/937 (40.9%)	312/756 (41.3%)	221/454 (48.7%)
25 to <30	354/937 (37.8%)	284/756 (37.6%)	160/454 (35.2%)
≥30 kg/m^2	179/937 (19.1%)	145/756 (19.2%)	60/454 (13.2%)
Smoking tobacco (ever)	809/1568 (51.6%)	660/1267 (52.1%)	413/795 (52.0%)
Smoking tobacco at GCA diagnosis	208/1563 (13.3%)	172/1263 (13.6%)	125/792 (15.8%)
Alcohol units/week	5 (0 to 7)	5 (0 to 7)	5 (0 to 7)
Alcohol ≥14 units/week	110/1147 (9.59%)	96/920 (10.4%)	58/565 (10.3%)
Index of Multiple Deprivation 2019 (quintiles)			
1 (most deprived)	270/1346 (20.1%)	187/885 (21.1%)	143/706 (20.3%)
2	269/1346 (20.0%)	176/885 (19.9%)	146/706 (20.7%)
3	269/1346 (20.0%)	173/885 (19.6%)	130/706 (18.4%)
4	269/1346 (20.0%)	182/885 (20.6%)	143/706 (20.3%)
5 (least deprived)	269/1346 (20.0%)	167/885 (18.9%)	144/706 (20.4%)

*Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.

ACR, American College of Rheumatology; AFR, African; BMI, body mass index; CV, cardiovascular disease; EAS, east Asian; EUR, white European (European/American); GCA, giant cell arteritis; N, sample number; PMR, polymyalgia rheumatica; IQR, interquartile range; SAS, South Asian.

Table 2

Patient demographics at presentation, categorised according to presence and type of ischaemic manifestations

	Cranial ischaemic complications (N† = 327/1925)	Transient cranial ischaemic features* (N† = 951/1604)	Extracranial ischaemic manifestations (N† = 203/1630)	No ischaemic manifestations (N† = 514/1944)
	MD (Q1–Q3) or N (%)			
Age at diagnosis (years)	72 (68–78)	71 (66–77)	69 (64–74)	71 (65–76)
Sex (female)	216/325 (66.5%)	675/948 (71.2%)	141/200 (70.5%)	351/513 (68.4%)
Ethnicity				
EUR	313/317 (98.7%)	909/915 (99.3%)	195/197 (98%)	501/504 (99.4%)
AFR	1/317 (0.3%)	1/915 (0.1%)	1/197 (0.5%)	0/504 (0%)
SAS	3/317 (1.0%)	5/915 (0.6%)	1/197 (0.5%)	3/504 (0.6%)
EAS	0/317 (0%)	0/915 (0%)	0/197 (0%)	0/504 (0%)
Family history of GCA	3/177 (1.7%)	10/389 (2.6%)	2/125 (1.6%)	12/336 (3.6%)
Family history of PMR	10/178 (5.6%)	20/387 (5.2%)	6/124 (4.8%)	11/328 (3.4%)
BMI (kg/m^2)				
<18.5	2/169 (1.2%)	8/384 (2.1%)	3/116 (2.6%)	8/333 (2.4%)
18.5 to <25	68/169 (40.2%)	173/384 (45.1%)	47/116 (40.5%)	123/333 (36.9%)
25 to <30	63/169 (37.3%)	131/384 (34.1%)	47/116 (40.5%)	136/333 (40.8%)
≥30 kg/m^2	36/169 (21.3%)	72/384 (18.8%)	19/116 (16.4%)	66/333 (19.8%)
Smoking tobacco (ever)	165/311 (53.1%)	368/700 (52.6%)	97/195 (49.7%)	227/460 (49.4%)
Smoking tobacco at GCA diagnosis	41/311 (13.2%)	91/700 (13%)	24/194 (12.4%)	62/456 (13.6%)
Alcohol units/week	4 (0 to 6)	5 (0 to 7)	4 (0 to 6)	5 (0 to 7)
Alcohol ≥14 units/week	21/218 (9.6%)	51/492 (10.4%)	14/149 (9.4%)	33/379 (8.7%)
Index of Multiple Deprivation 2019 (quintiles)				
1 (most deprived)	45/209 (21.5%)	137/678 (20.2%)	35/169 (20.7%)	63/353 (17.9%)
2	43/209 (20.6%)	132/678 (19.5%)	34/169 (20.1%)	73/353 (20.7%)
3	34/209 (16.3%)	141/678 (20.8%)	38/169 (22.5%)	78/353 (22.1%)
4	50/209 (23.9%)	139/678 (20.5%)	39/169 (23.1%)	61/353 (17.3%)
5 (least deprived)	37/209 (17.7%)	129/678 (19.0%)	23/169 (13.6%)	78/353 (22.1%)

AFR, African; BMI, body mass index; CV, cardiovascular; EAS, east Asian; EUR, white European (European/American); GCA, giant cell arteritis; MD, median; N, sample number; PMR, polymyalgia rheumatica; Q, quartile; SAS, South Asian.

* Omitting individuals with cranial ischaemic complications.

† Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.

Table 3
Patient clinical characteristics at presentation: cranial ischaemic complications; transient cranial ischaemic features; extra-cranial ischaemic manifestations

	Cranial ischaemic complications	Transient cranial ischaemic features*	Extracranial ischaemic manifestations	No ischaemic features
	(N† = 327/1925) MD (Q1–Q3) or N (%)	(N† = 951/1604)	(N† = 203/1630)	(N† = 514/1944)
GCA symptoms to steroids duration (days)	44 (4–58)	49 (7–61)	69 (13–92)	39 (7–50)
Cranial ischaemic manifestations‡				
Cranial ischaemic complications	327/327 (100.0%)	0/938 (0%)	49/201 (24.4%)	0/514 (0%)
Ocular complications	297/327 (90.8%)	0/942 (0%)	38/199 (19.1%)	0/510 (0%)
Non-ocular cranial complications	42/295 (14.2%)	0/948 (0%)	14/181 (7.7%)	0/439 (0%)
Transient cranial ischaemic features*	0/325 (0%)	951/951 (100%)	93/154 (60.4%)	0/514 (0%)
Ocular ischaemic features*	0/327 (0%)	423/942 (44.9%)	40/199 (20.1%)	0/510 (0%)
Non-ocular cranial ischaemic features*	0/321 (0%)	768/948 (81%)	78/153 (51%)	0/504 (0%)
Extracranial ischaemic manifestations				
Extracranial ischaemic features§	43/275 (15.6%)	92/598 (15.4%)	192/203 (94.6%)	0/435 (0%)
Extracranial ischaemic complications¶	6/300 (2.2%)	1/746 (0.2%)	11/203 (5.4%)	0/514 (0%)
PMR and polymyalgic symptoms**	80/298 (26.9%)	263/666 (35.4%)	87/188 (46.3%)	143/437 (32.7%)
Before GCA	51/80 (63.8%)	146/236 (61.9%)	57/87 (65.5%)	104/143 (72.7%)
At GCA presentation	21/80 (26.3%)	90/236 (38.1%)	30/87 (34.5%)	39/143 (27.3%)
Systemic inflammatory response				
Weight loss/kg	0.7 (−1.0 to 4.0)	0.3 (−2.0 to 3.4)	−0.2 (−3.9 to 4.8)	−0.08 (−2.15 to 3.0)
Weight loss≥4 kg	81/154 (52.6%)	151/327 (46.2%)	62/119 (52.1%)	104/279 (37.3%)
ESR mm/hour	58 (32–86)	64 (36–93)	59.9 (33–88)	61 (34–87)
CRP mg/L	67 (13–107)	75 (20–109)	73 (19–110)	67 (17–96)
Platelet count, $\times 10^9$/L	369 (274–447)	398 (302–468)	390 (291–456)	368 (278–439)

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; MD, median; PMR, polymyalgia rheumatica; Q, quartile.
* Omitting individuals with cranial ischaemic complications.
† Sample size varied in different analyses due to missing clinical data. The N in this column reflects the individuals included in the various analyses.
‡ Cranial ischaemic manifestations at GCA presentation. (A) Transient cranial ischaemic features. Ocular ischaemic features: transient diplopia; transient double vision/absence of ocular motility; transient field defect; transient reduced acuity; transient vision loss. Non-ocular cranial ischaemic features: jaw claudication; tongue claudication; transient ischaemic attack at presentation considered secondary to GCA. (B) Cranial ischaemic complications. Ocular complications: Anterior ischaemic optic neuropathy; branch retinal artery occlusion; cilioretinal artery occlusion; cranial nerve palsy (III, IV or V); central retinal artery occlusion; posterior ischaemic optic neuropathy; relative afferent pupillary defect; irreversible visual loss; irreversible visual field defect; irreversible ocular motility; irreversible diplopia. Non-ocular cranial complications: Scalp necrosis; tongue necrosis; cerebrovascular accident at presentation considered secondary to GCA.
§ Extracranial ischaemic features: arm claudication; leg claudication.
¶ Extracranial ischaemic complications: fixed vascular stenosis to limb at presentation, secondary to GCA.
** PMR and polymyalgic symptoms: Polymyalgic symptoms and/or a formal PMR diagnosis were recorded at the time of initial GCA diagnosis. Where PMR was diagnosed and treated with medium-dose glucocorticoids (eg, 10–20 mg prednisolone) prior to developing symptoms of GCA we classified these cases as having PMR prior to GCA, whereas untreated symptoms at GCA presentation were recorded as occurring at GCA presentation.

age at GCA diagnosis (OR 1.54, 95% CI 0.87 to 2.74, $p = 2.00\times10^{-3}$, for the highest (≥80 years) vs lowest (<60 years) decade), PMR symptoms at GCA diagnosis (OR (95% CI) = 0.73 (0.56 to 0.95), p = 0.02), and weight loss ≥4 kg (OR (95% CI) = 1.54 (1.08 to 2.19), p = 0.08). The CVD composite (OR (95% CI) = 1.68 (1.27 to 2.22), $p < 1.00\times10^{-3}$), hypertension (OR (95% CI) = 1.59 (1.24 to 2.05), $p < 1\times10^{-3}$), hyperlipidaemia (OR (95% CI) = 1.5 (1.15 to 1.96), $p = 3.00\times10^{-3}$), cholesterol-lowering medication pre-GCA (OR (95% CI) = 1.38 (1.03 to 1.84), p = 0.03) and antiplatelet therapy pre-GCA (OR (95% CI) = 1.42 (1.02 to 1.99), p = 0.04) were also each associated with cranial ischaemic complications in GCA.

An additional two risk factors had an LR p<0.1: platelet count (OR (95% CI) = 0.61 (0.41 to 0.91), p = 0.06, for the highest vs lowest quintile) and anticoagulant therapy pre-GCA (OR (95% CI) = 0.5 (0.22 to 1.10), p = 0.06). 29/435 (6.7%) presenting without any ischaemic features were on anticoagulant therapy, whereas only 7/280 (2.5%) GCA patients presenting with cranial ischaemic complications were on anticoagulant therapy (online supplemental table 6).

Sensitivity analyses were performed whereby individuals with transient cranial ischaemic features or extracranial ischaemic manifestations were removed from the primary reference cohort, and univariable analyses were re-evaluated, excluding up to N = 997 reference subjects. Several risk factors remained associated with cranial ischaemic complications in GCA at LR p<0.05 (table 4). These included age at GCA diagnosis (OR (95% CI) = 1.62 (0.85 to 3.09), $p < 1.00\times10^{-3}$, for the highest (≥80 years) vs lowest (<60 years) decade), weight loss ≥4 kg (OR (95% CI) = 1.85 (1.24 to 2.75), $p = 2.00\times10^{-3}$), the CVD composite (OR (95% CI) = 1.42 (1.01 to 2.00), p = 0.04), hypertension (OR (95% CI) = 1.54 (1.16 to 2.05), $p = 3.00\times10^{-3}$), antiplatelet therapy (OR (95% C) = 1.48 (1.00 to 2.20), p = 0.05) and anticoagulant therapy (OR (95% CI) = 0.38 (0.16 to 0.87), p = 0.01).

Elastic net regression was performed on risk factors with an LR p<0.1 (n = 13) to remove redundant or highly correlated variables from the model and to perform variable selection. The weight loss (≥4 kg) variable was omitted from regression due to low sample numbers with non-missing data (N samples with non-missing data for weight loss variable = 681). Full details of model optimisation, including alpha and lambda selection, and variable weights as determined by elastic net regression (online supplemental table 14), are described in online supplemental results. The 11 variables prioritised by elastic net regression were tested in multivariable regression (sample N = 789), adjusted for clinical and sociodemographic risk factors (table 5). This revealed two statistically significant associations with

Table 4
Univariable associations with cranial ischaemic complications with likelihood ratio p≤0.1

	Primary univariable associations			Sensitivity analyses*		
Trait	OR (95% CIs)	P value†	DF	OR (95%CIs)	P value†	DF
Age at GCA diagnosis‡		2.00×10^{-3}	1899		8.17×10^{-4}	909
<60 years	1.00			1.00		
60 to <70 years	0.99 (0.57 to 1.71)			0.95 (0.52 to 1.74)		
70 to <80 years	1.43 (0.84 to 2.43)			1.63 (0.91 to 2.92)		
≥80 years	1.54 (0.87 to 2.74)			1.66 (0.87 to 3.17)		
PMR symptoms	0.73 (0.56 to 0.95)	0.02	1529	0.86 (0.64 to 1.17)	0.33	789
Weight loss (≥4 kg)	1.54 (1.08 to 2.19)	0.02	797	1.85 (1.24 to 2.75)	2.00×10^{-3}	437
ESR quintiles (mm/hour)‡		0.09	1200		0.57	654
<29	1.00			1.00		
29 to <49	0.57 (0.36 to 0.91)			0.60 (0.36 to 1.00)		
49 to <69	1.08 (0.71 to 1.64)			1.29 (0.80 to 2.08)		
69 to <96	0.69 (0.44 to 1.08)			0.76 (0.46 to 1.26)		
≥96	0.67 (0.43 to 1.04)			0.82 (0.50 to 1.34)		
Platelet count quintiles ($\times10^9$/L)‡		0.06	1507		0.69	770
<271	1.00			1.00		
271 to <334.8	0.65 (0.44 to 0.96)			0.78 (0.50 to 1.22)		
334.8 to <396	0.67 (0.45 to 0.99)			0.81 (0.52 to 1.27)		
396 to <485	0.89 (0.61 to 1.29)			1.20 (0.78 to 1.84)		
≥485	0.61 (0.41 to 0.91)			0.90 (0.57 to 1.42)		
CVD composite	1.68 (1.27 to 2.22)	$<1\times10^{-3}$	1924	1.52 (1.11 to 2.10)	0.01	930
TIA/CVA	1.64 (1.06 to 2.52)	0.03	1550	1.78 (1.06 to 2.99)	0.03	801
Hyperlipidaemia	1.50 (1.15 to 1.96)	3.00×10^{-3}	1545	1.62 (1.19 to 2.21)	2.00×10^{-3}	810
Hypertension	1.59 (1.24 to 2.05)	$<1.00\times10^{-3}$	1616	1.53 (1.15 to 2.03)	4.00×10^{-3}	827
Antiplatelet therapy	1.42 (1.02 to 1.99)	0.04	1321	1.48 (1.00 to 2.2)	0.05	682
Anticoagulant therapy	0.50 (0.22 to 1.10)	0.06	1398	0.38 (0.16 to 0.87)	0.01	733
Cholesterol-lowering medication	1.38 (1.03 to 1.84)	0.03	1316	1.38 (0.99 to 1.93)	0.06	678
Platelet count PRS quintiles‡		0.09	1843		0.17	891
1 (lowest)	1.00			1.00		
2	0.83 (0.57 to 1.21)			0.69 (0.45 to 1.06)		
3	0.69 (0.47 to 1.03)			1.03 (0.68 to 1.56)		
4	1.06 (0.73 to 1.54)			0.80 (0.53 to 1.21)		
5 (highest)	1.02 (0.70 to 1.48)			0.69 (0.45 to 1.06)		
TIA PRS quintiles‡		0.027	1842		0.098	891
1 (lowest)	1			1		
2	0.98 (0.66 to 1.47)			0.75 (0.48 to 1.17)		
3	1.25 (0.85 to 1.85)			1.03 (0.66 to 1.62)		
4	0.97 (0.64 to 1.45)			0.78 (0.49 to 1.24)		
5 (highest)	1.37 (0.93 to 2)			1.22 (0.79 to 1.90)		

CVA, cerebrovascular attack; CVD, cardiovascular disease; DF, degrees of freedom; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; PRS, Polygenic Risk Score; TIA, transient ischaemic attack.
* Sensitivity analyses include a reference group with no ischaemic features.
† P value from likelihood ratio test.
‡ Analyses performed using continuous variables, quantile/group ORs presented for interpretation purposes.

cranial ischaemic complications in GCA: age at GCA diagnosis (adjusted OR (95% CI) = 1.85 (0.84 to 4.32), $p = 2.81\times10^{-3}$, for the highest (≥80 years) vs lowest (<60 years) decade) and anticoagulant therapy prior to GCA (adjusted OR (95% CI) = 0.18 (0.04 to 0.53), $p = 1.09\times10^{-3}$).

To assess associations between CVDs/CV risk factors and cranial ischaemic complications in GCA without the confounding influence of age, PRS for these traits were tested for association with GCA in univariable analyses (online supplemental table 15), revealing one PRS with an LR p<0.05 (table 4), a transient ischaemic attack (TIA) PRS (OR (95% CI) = 1.37 (0.93 to 2.00), p = 0.03, for the highest compared with the lowest PRS quintile) and one PRS with an LR p<0.1, a platelet count PRS (OR (95%I) = 1.02 (0.70 to 1.48), p = 0.09).

PRSs with an LR p<0.10 were added to the clinical and sociodemographic model, elastic net regression was performed for variable selection (online supplemental table 16), and multivariable regression was performed on the final clinical, sociodemographic and genetic model (N = 812). The two variables associated with cranial ischaemic complications prior to the addition of PRS remained significant and retained similar effect sizes compared with the model without PRS (table 5): age at GCA diagnosis (adjusted OR (95% CI) = 1.60 (0.73 to 3.66), $p = 2.52\times10^{-3}$, for the highest (≥80 years) vs lowest (<60 years) decade) and anticoagulant therapy pre-GCA (adjusted OR (95% CI) = 0.21 (0.05 to 0.62), $p = 4.95\times10^{-3}$). Both of these variables remained strongly associated with cranial ischaemic complications in women, but not men, in sex-stratified analyses (online supplemental table 17), as well as in analyses performed using solely patients who fulfilled the 2022 ACR/EULAR classification criteria (online supplemental table 18). Of note, the platelet count PRS was also strongly associated with the outcome in this analysis (AOR (95% CI) = 0.41 (0.22 to 0.73), p = 0.04), suggesting a potentially protective role of increased heritable platelet levels in cranial ischaemic complications.

Details of associations with secondary outcomes may be found in online supplemental table 19. Briefly, no variables had an association with transient cranial ischaemic complications at LR p<0.05. Associations were found between extracranial ischaemic manifestations and PMR symptoms at GCA diagnosis

Table 5
Multivariable associations with cranial ischaemic complications in GCA at presentation (complete case approach), following variable selection with elastic net regression

	Model including clinical and sociodemographic variables		Model including clinical, sociodemographic and PRS variables	
Trait	OR (95% CIs)	P value*	OR (95% CIs)	P value*
Age at diagnosis†		2.81×10^{-3}		2.52×10^{-3}
<60 years	1.00		1.00	
60 to <70 years	0.70 (0.34 to 1.55)		0.58 (0.28 to 1.25)	
70 to <80 years	1.21 (0.60 to 2.62)		1.06 (0.54 to 2.23)	
≥80 years	1.85 (0.84 to 4.32)		1.60 (0.73 to 3.66)	
PMR	0.76 (0.52 to 1.10)	0.13	0.80 (0.55 to 1.16)	0.26
ESR quintiles (mm/hour)†		0.29		0.24
<29	1.00		1.00	
29 to <49	0.54 (0.29 to 1.00)		0.49 (0.27 to 0.90)	
49 to <69	1.30 (0.73 to 2.31)		1.13 (0.66 to 1.95)	
69 to <96	0.69 (0.37 to 1.27)		0.62 (0.34 to 1.10)	
≥96	0.69 (0.37 to 1.29)		0.63 (0.36 to 1.11)	
Platelet count quintiles ($\times10^9$/L)†		0.70	NA‡	
<271	1.00			
271 to <334.8	0.61 (0.35 to 1.08)			
334.8 to <396	0.56 (0.30 to 1.04)			
396 to <485	0.93 (0.52 to 1.66)			
≥485	0.63 (0.34 to 1.17)			
CVD composite	1.41 (0.81 to 2.41)	0.23	1.13 (0.65 to 1.93)	0.72
TIA/CVA	1.20 (0.57 to 2.52)	0.72	1.34 (0.62 to 2.82)	0.50
Hyperlipidaemia	1.61 (1.02 to 2.54)	0.11	1.44 (0.90 to 2.26)	0.33
Hypertension	1.47 (1.01 to 2.14)	0.07	1.34 (0.93 to 1.95)	0.11
Antiplatelet therapy	1.19 (0.70 to 1.98)	0.66	1.25 (0.73 to 2.10)	0.43
Anticoagulant therapy	0.18 (0.04 to 0.53)	1.09×10^{-3}	0.21 (0.05 to 0.62)	4.95×10^{-3}
Cholesterol-lowering therapy	0.60 (0.36 to 0.98)	0.14	0.68 (0.41 to 1.12)	0.24
Platelet count PRS quintiles†	NA			0.11
1			1	
2			0.55 (0.31 to 0.94)	
3			1.03 (0.6 to 1.75)	
4			0.69 (0.41 to 1.17)	
5			0.45 (0.25 to 0.81)	
TIA PRS quintiles†	NA			0.13
1			1	
2			0.99 (0.55 to 1.76)	
3			1.21 (0.67 to 2.19)	
4			1.05 (0.59 to 1.87)	
5			1.29 (0.74 to 2.26)	

CVA, cerebrovascular accident; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; NA, not available; PMR, polymyalgia rheumatica; PRS, Polygenic Risk Score; TIA, transient ischaemic attack.
* P value from likelihood ratio test.
† Analyses performed using continuous variables, quantile/group ORs presented for interpretation purposes.
‡ Platelet count was not retained by elastic net regression for this round of analyses, see online supplemental results.

(adjusted OR (95% CI) = 1.99 (1.21 to 3.29), p = 0.01) and the CVD composite (adjusted OR (95% CI) = 2.39 (1.17 to 4.75), $p = 5.2\times10^{-3}$).

Positional mapping of the TIA PRS using Ensembl V.11 [26] and ANNOVAR [27] revealed 17 mapped loci (16 protein-coding genes), including the *MROH9, CD96, IBTK, CLTA, TEK* and *KLB* genes (figure 1).

Sensitivity analysis

A sensitivity analysis was performed on the clinical and sociodemographic multivariable model, omitting the 'anticoagulant use prior to GCA' variable and reperforming elastic net regression for variable selection. Following this, three variables remained in the multivariable model (complete case N = 1429), of which two were statistically significant (table 6): age at diagnosis (adjusted OR (95% CI) = 1.03 (1.01 to 1.04), $p = 4.15\times10^{-3}$) and hypertension (adjusted OR (95% CI) = 1.35 (1.03 to 1.75), p = 0.03). When PRSs were added to the sensitivity analysis model (omitting the anticoagulant use prior to GCA variable) and elastic net was performed (complete case N = 1545), three variables remained in the model including age at diagnosis (adjusted OR (95% CI) = 1.25 (0.69 to 2.34), p = 0.01, for the highest (≥80 years) vs lowest (<60 years) decade), hypertension (adjusted OR (95% CI) = 1.53 (1.18 to 1.98), $p = 1.17\times10^{-3}$) and platelet count PRS (adjusted OR (95% CI) = 0.63 (0.42 to 0.93), p = 0.10).

DISCUSSION

Using the largest cohort of well-characterised GCA patients recruited from secondary care to date (N = 1946), the univariable analysis identified 10 variables significantly associated with cranial ischaemic complications at GCA presentation. The large sample size permitted multivariable analysis, which identified that advanced age was a risk factor and anticoagulant therapy protective, following adjustment for all the other included variables. If anticoagulant therapy was removed from the multivariable model, age and hypertension remained in the model as significantly associated with cranial ischaemic complications. Positional gene mapping of an associated TIA PRS revealed loci in genes related to immune and coagulation pathways.

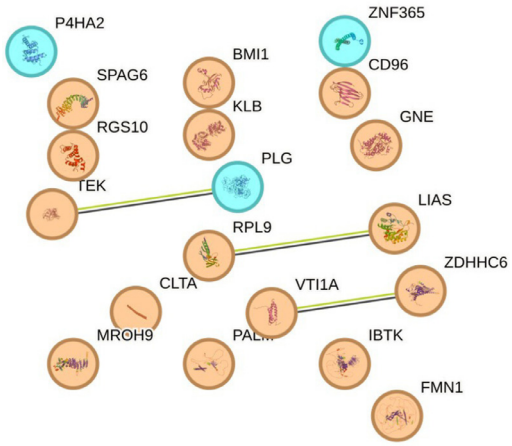

Figure 1. StringDB[28] network analysis using proteins (nodes) encoded by positionally mapped genes of TIA PRS loci (orange nodes) and proteins encoded by positionally mapped loci from previous work (blue nodes).[23,29] Edges of this network represent protein-protein links found by StringDB via text mining (green edges) and coexpression (black edges). BMI1, BMI1 Proto-Oncogene, Polycomb Ring Finger; CD96, Cluster of Differentiation 96; CLTA, Clathrin Light Chain A; FMN1, Formin 1; GNE, Glucosamine (UDP-N-Acetyl)−2-Epimerase/N-Acetylmannosamine Kinase; IBTK, Inhibitor Of Bruton Tyrosine Kinase; KLB, Beta-Klotho; LIAS, Lipoic Acid Synthetase; MROH9, Maestro Heat Like Repeat Family Member 9; PALM, Paralemmin; PLG, Plasminogen; P4HA2, Prolyl 4-Hydroxylase Subunit Alpha 2; RGS10, Regulator of G Protein Signalling 10; RPL9, Ribosomal Protein L9; SPAG6, Sperm Associated Antigen 6; TEK, Tyrosine Kinase; VTI1A, Vesicle Transport Through Interaction With T-SNAREs 1A; ZDHHC6, Zinc Finger DHHC-Type Containing 6; ZNF365, Zinc Finger Protein 365.

The present work confirms the association of cranial ischaemic complications with increasing age [3,5] and additionally identifies a potential protective effect of anticoagulant use, but not antiplatelet use, prior to GCA diagnosis. The use of antiplatelet drugs was strongly associated with age in our study and larger studies are required to disentangle any potential beneficial effects of antiplatelet medication from the effects of age. Small studies initially suggested a protective effect of antiplatelet/anticoagulant) therapy against ischaemic events in GCA [11,12] but meta-analysis failed to confirm this clearly [10]. Currently, due to the lack of randomised controlled trial data, neither antiplatelet nor anticoagulant therapy is universally recommended for patients with GCA [2]. As expected, anticoagulant use was correlated with AF. The lack of association of AF with ischaemic complications in univariable analyses, and clinical implausibility of a protective effect of AF against ischaemic manifestations, makes this an unlikely source of confounding. Nor does confounding by other CV risk factors appear likely. It is difficult to entirely control for confounding by indication: it is possible that an unmeasured confounder (such as prothrombotic tendency reflected in the history of thromboembolic disease) may be influencing results. Nonetheless, the effect size observed in this study in relation to anticoagulation is striking and suggests that further exploration is warranted to determine whether there may be a direct beneficial effect of anticoagulation in GCA.

Inflammation-induced thrombosis is widely recognised in the vasculitides [30]. While thrombosis is infrequently observed in the temporal arteries in GCA, it is unclear whether thrombosis occurs in the smaller vessels supplying the eye. GCA is associated with venous thromboembolism, particularly during active disease [31]. A number of small studies have reported antiphospholipid antibodies (lupus anticoagulant and IgG anti-cardiolipin, β2-glycoprotein I and prothrombin antibodies) in up to 48% of GCA cases [32–34]. In one study, there was a suggestion that two or more antiphospholipid antibodies were associated with visual manifestations [34], but this requires confirmation. Genetic associations with *PLG* have been demonstrated [23,29]. *PLG* encodes plasminogen, the precursor of plasmin, which lyses fibrin clots as well as inactivating coagulation factors (thereby acting as an anticoagulant) [35,36]. A recent report suggests that overproduction of reactive oxygen species by peripheral blood leucocytes in GCA results in the oxidation of fibrinogen [37]; this, in turn, causes a striking impairment of fibrinogen function such that it becomes less susceptible to fibrinolysis by plasmin; this functional impairment was reversed in vitro by tocilizumab. Taken together with the present findings, this provides a plausible mechanism linking immune and thrombotic pathways in GCA, providing new perspectives on therapy.

Further studies are now required to explore the role of thrombosis in cranial ischaemic manifestations, to determine whether

Table 6
Associations with cranial ischaemic complications in GCA at presentation, adjusted for sociodemographic, clinical and genetic factors, following variable selection with elastic net regression

Trait	Model including clinical and sociodemographic variables		Model including clinical, sociodemographic and PRS variables	
	OR (95% CI)	P value*	OR (95%CI)	P value*
Age at GCA diagnosis†		4.15×10^{-3}		0.01
<60 years	1.00		1.00	
60 to <70 years	0.83 (0.48 to 1.49)		0.85 (0.49 to 1.53)	
70 to <80 years	1.25 (0.74 to 2.22)		1.29 (0.77 to 2.29)	
≥80 years	1.33 (0.73 to 2.49)		1.25 (0.69 to 2.34)	
PMR	0.78 (0.59 to 1.02)	0.07	NA	
Hypertension	1.35 (1.03 to 1.75)	0.03	1.53 (1.18 to 1.98)	1.17×10^{-3}
Platelet count PRS Quintiles†	NA			0.10
1			1.00	
2			0.59 (0.39 to 0.88)	
3			0.88 (0.60 to 1.29)	
4			0.70 (0.47 to 1.03)	
5			0.63 (0.42 to 0.93)	

Sensitivity analysis omitting anticoagulant use prior to GCA.
CVD, cardiovascular disease; GCA, giant cell arteritis; NA, not available; PMR, polymyalgia rheumatica; PRS, Polygenic Risk Score.
* P value from likelihood ratio test.
† Analyses performed using continuous variables, quantile/group ORs presented for interpretation purposes.

short-term anticoagulant therapy in combination with glucocorticoid use could reduce the risk of complications in high-risk GCA patients. Patients presenting with visual symptoms, particularly those with monocular blindness or amaurosis fugax, are at elevated risk of further visual loss shortly after GCA diagnosis [38]. This is illustrated by an orbital MRI study that showed that 38% of patients with unilateral visual symptoms had MRI abnormalities of the contralateral eye [39], illustrating a potential window of opportunity to prevent bilateral blindness.

Given the relatively small number of patients taking an anticoagulant prior to GCA diagnosis, we sought to determine if other risk factors may also be relevant for those not using anticoagulants. These secondary analyses revealed the importance of both age and hypertension in fully adjusted models. An association between severe ischaemic complications and hypertension was observed in previous studies [6,40]. While involvement of the renal arteries is traditionally viewed to be a more typical feature of Takayasu arteritis, imaging studies have shown up to 16% of patients with large vessel GCA have evidence of renal artery involvement [41].

To gain further mechanistic insight, a PRS constructed for TIA had a statistically significant association (LR $p<0.05$) with cranial ischaemic complications in univariate analyses, yet the strength of this association was reduced following adjustment for clinical, sociodemographic and genetic risk factors. Positional mapping of this PRS with Ensembl [26] and ANNOVAR [27] revealed genetic variants localised to 16 protein-coding genes in the genome. These loci included *TEK*, which encodes the angiopoietin-1 receptor (TIE2), known to be elevated in GCA [42]. TIE2 is instrumental in cell surface interactions at the vascular wall and is implicated in haemostasis pathways shared with plasminogen [23,43]. Plasminogen is thought to act in multiple haemostasis pathways: first in platelet activation, signalling and aggregation, a cascade in which the procoagulant properties of platelets (which contain angiogenesis stimulators and inhibitors) are enhanced and thrombus formation occurs [44], and second in the dissolution of fibrin clots, which includes tissue remodelling, cell migration and inflammation [36]. The presence of GCA susceptibility and GCA outcome associations in genes which encode proteins implicated in these haemostasis-related and coagulation-related pathways further supports the potential importance of these pathways in GCA pathogenesis.

Limitations

While the size of this GCA cohort (N = 1946) is the largest with detailed clinical characterisation reported to date, the use of a complete case design in this work and the interrogation of disease subsets reduces the number of samples, cutting statistical power. Another limitation is that this cohort was primarily Caucasian. Although the prevalence of GCA is high in northern European countries, many reports confirm that GCA can occur in non-Caucasian individuals. The lack of representation of non-Caucasian populations in this work therefore limits the application of findings from the study to individuals from other ethnic groups. This is particularly prudent for PRS associations found in this work, since patterns of linkage disequilibrium vary across ethnicities and SNP associations found for one population may not be relevant to another. It is also important to note that PRS may include some genetic variants that are not genuine predictors of the outcome for which the PRS is optimised (eg, TIA). However, optimal PRS tend to yield sufficient true associations to outweigh those included due to stochastic variation, meaning that over-representation of biological pathways in PRS should still be indicative of possible functional relevance.

Covariates included in multivariable analyses must be chosen carefully when looking for evidence of causal relationships, to avoid overadjustment [45]. For example, hypertension influences both AF and anticoagulant prescribing decisions; therefore, if seeking to investigate the causal role of hypertension, adjustment for anticoagulant therapy might distort estimates of the causal effect of hypertension on cranial ischaemic complications in GCA and reduce power to detect association, especially if anticoagulant therapy has its own direct effect on the outcome. The sensitivity analyses omitting anticoagulant therapy in part address this limitation.

Finally, current GCA guidelines advise the use of at least one diagnostic test (eg, TAB or imaging) to confirm GCA, in order to avoid misdiagnosis of non-arteritic anterior ischaemic optic neuropathy (AION) (which constitutes approximately 95% of all AION) as arteritic-AION [2,46]. Given that 30.8% of this cohort, presenting over three decades, did not have a confirmatory diagnostic test, it is possible that some individuals in this cohort were misdiagnosed with GCA. A number of sensitivity analyses were performed, including analyses of biopsy or imaging-confirmed GCA.

CONCLUSION

This work identified risk factors associated with cranial ischaemic complications in GCA, which included age at diagnosis, hypertension and a potentially protective role of anticoagulant therapy in severe complications in GCA. It must be emphasised that, since unmeasured confounding could not be ruled out, these findings are not sufficient yet to change clinical practice; further research, such as randomised controlled trials. Positional gene mapping of an associated TIA PRS also highlighted genetic loci related to immune and coagulation pathways. Together, these results suggest a need for further interrogation of the role of thrombosis in GCA, and to elucidate whether anticoagulant therapy alongside glucocorticoids might be beneficial in patients with GCA, especially those with transient or monocular visual involvement, or other high-risk subsets.

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NJMC was responsible for the analysis planning, data collection, verification, data analysis, data interpretation and manuscript writing of analyses in this work. CJH, LS and HRM contributed to the data collection and verification in this work. MMI contributed to the quality control of genetic data in this work. AWM (guarantor) and MMI contributed to the study conception, design, data interpretation and drafting of this work and all authors contributed to the critical revision of the article and approved the final submitted version. CJH, LS and HRM are joint second authors.

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None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

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This study involves human participants and was approved by Yorkshire and the Humber Leeds West Research Ethics Committee (05/Q1108/28). Participants gave informed consent to participate in the study before taking part.

Data availability statement

Data are available on reasonable request. Data access requests should be directed to the corresponding author. UK Biobank data may be accessed by completing an application at https://www.ukbiobank.ac.uk/. Generated PRS is available on request.

Supplementary materials

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