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BRIEF REPORT

Association of Somatic *TET2* Mutations With Giant Cell Arteritis

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Objective. Giant cell arteritis (GCA) is an age-related vasculitis. Prior studies have identified an association between GCA and hematologic malignancies (HMs). How the presence of somatic mutations that drive the development of HMs, or clonal hematopoiesis (CH), may influence clinical outcomes in GCA is not well understood.

Methods. To examine an association between CH and GCA, we analyzed sequenced exomes of 470,960 UK Biobank (UKB) participants for the presence of CH and used multivariable Cox regression. To examine the clinical phenotype of GCA in patients with and without somatic mutations across the spectrum of CH to HM, we performed targeted sequencing of blood samples and electronic health record review on 114 patients with GCA seen at our institution. We then examined associations between specific clonal mutations and GCA disease manifestations.

Results. UKB participants with CH had a 1.48-fold increased risk of incident GCA compared to UKB participants without CH. GCA risk was highest among individuals with cytopenia (hazard ratio [HR] 2.98, $P = 0.00178$) and with *TET2* mutation (HR 2.02, $P = 0.00116$). Mutations were detected in 27.2% of our institutional GCA cohort, three of whom had HM at GCA diagnosis. *TET2* mutations were associated with vision loss in patients with GCA (odds ratio 4.33, $P = 0.047$).

Conclusions. CH increases risk for development of GCA in a genotype-specific manner, with the greatest risk being conferred by the presence of mutations in *TET2*. Somatic *TET2* mutations likewise increase the risk of GCA-associated vision loss. Integration of somatic genetic testing in GCA diagnostics may be warranted in the future.

INTRODUCTION

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis that affects people over the age of 50.[1] Because of the risk of permanent vision loss caused by ischemic damage to the ophthalmic vasculature, GCA is a medical emergency that requires rapid recognition and treatment with high-dose steroids. Interleukin (IL)-6R blockade with tocilizumab is currently

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the only US Food and Drug Administration–approved steroid-sparing therapy.[1]

GCA-initiating events are largely unknown, but myeloid cell activation may play a central role based on translational, pathologic, and epidemiologic studies.[1] In patients with GCA, circulating monocytes express elevated levels of *IL6* and *IL1B* and are the primary hematopoietic source of systemically elevated IL-6, and neutrophil expansion is the most common cellular abnormality in untreated disease.[1–3] Myeloid neoplasms (MNs) are also associated with GCA. In retrospective studies of patients with inflammatory features of myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML), vasculitis is the most common diagnosis, and GCA is the most frequent vasculitis subtype observed.[4,5]

Clonal hematopoiesis (CH) describes the age-related expansion of a clonal population of hematopoietic stem cells and their progeny that are detectable using next-generation sequencing, typically after age 50 years. CH is often caused by somatic mutations in MN driver genes. When the variant allele fraction (VAF) is ≥0.02 without evidence of hematologic malignancy (HM), the terms clonal hematopoiesis of indeterminant potential (CHIP) and clonal cytopenia of uncertain significance (CCUS) are used to refer to patients without and with unexplained cytopenia, respectively.[6] CHIP and CCUS have variable risk of evolution to overt myeloid malignancies, including MDS, CMML, and acute myeloid leukemia, with risk determined by hematologic and molecular features.[7]

Along with increased risk of MN, patients with CHIP and CCUS have elevated mortality from ischemic cardiovascular disease and develop other age-associated inflammatory diseases.[8] Although risk of MN is known to be genotype-dependent, genotype-specific risks for inflammatory diseases are emerging.[8] Mutations in the epigenetic modifier *TET2* may confer a particular risk for inflammatory sequalae, as suggested by retrospective human data and preclinical mouse models that have linked *Tet2*-mutated CHIP and CCUS to ischemic cardiovascular disease, gout, chronic liver disease, and several other inflammatory diseases via myeloid activation.[8–10]

Because of the shared associations of CH and GCA with older age and MN as well as mutual evidence of myeloid activation, we hypothesized that CHIP and CCUS would be associated with incident GCA. We further sought to investigate whether the presence of somatic mutations, especially in *TET2*, would influence adverse outcomes in patients with GCA, including incident vision loss and HM. To test this hypothesis, we analyzed data from the UK Biobank (UKB), a large population dataset, and a separate cohort of patients with GCA with deep clinical annotation from our own institution.

METHODS

UKB cohort. UKB data were extracted under application 50834 from a cohort of 502,490 healthy adults 40 to 70 years of age recruited between 2006 to 2010. Whole exome sequencing data were analyzed for CHIP-defining somatic mutations as previously described.[10] Individuals with low abundance clones (VAF < 0.02), missing laboratory values, and MN diagnosed before or up to six months following study enrollment were excluded from this analysis. After exclusions, 470,960 individuals were eligible for study inclusion, including 29,835 with CHIP or CCUS and 441,125 without CHIP or CCUS (Supplementary Figure 1). Incident GCA was identified using linked electronic medical record (EMR) data and *International Classification of Diseases, Tenth Revision* (ICD-10) codes M31.5 and M31.6.

Massachusetts General Brigham GCA cohort. The Massachusetts General Brigham (MGB) cohort of GCA includes 114 individuals who received longitudinal care at MGB; 99% of cases met 2022 American College of Rheumatology (ACR)/EULAR GCA Classification Criteria.[11] The cohort was identified through ICD-10 codes M31.5 and M31.6 in a search of the MGB Biobank, which has banked DNA samples from >80,000 adults across the MGB health care system in Boston, Massachusetts. EMR abstraction of 387 individuals revealed 98 had positive temporal artery biopsy, imaging diagnosis of GCA, or clinical diagnosis meeting 1990 ACR GCA Classification criteria[12] diagnosed by a clinical rheumatologist within six years of blood sample collection. The second portion of the cohort (n = 16) was prospectively recruited at time of temporal artery biopsy from Massachusetts Eye and Ear Infirmary and Brigham and Women's Hospital. EMR abstraction, masked to genetic data, was performed to annotate patient demographics, GCA outcomes, medication use, blood counts, referral to hematology, and development of HM. Targeted next-generation sequencing, alignment, and genetic variant calling were performed as previously described[13] using the Illumina platform and libraries generated with two custom hybrid capture probe sets from Twist Biosciences. All participants provided written informed consent to participate in biobanking. The Institutional Review Board of MGB gave ethical approval for biobanking and EMR abstraction protocols. For extended details on cohort identification, EMR abstraction, and sequencing methods, see Supplementary Methods.

Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/art.42738).

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Cell sorting and DNA extraction. Cryopreserved peripheral blood mononuclear cells (PBMCs) were available from four prospectively recruited individuals with somatic mutations and were sorted into cell fractions as previously described.[14] For gating strategy and reagents, see Supplementary Methods. The QIAamp DNA Blood Mini kit (Qiagen, 51104) and the Zymo DNA Microprep Kit (D3021) were used for DNA extraction from bulk and sorted samples, respectively.

Statistical analyses. Statistical analyses and figure preparation were performed using R (R Foundation for Statistical Computing) and GraphPad Prism (GraphPad Software). Wilcoxon rank sum test and Fisher's exact tests were used to evaluate continuous and categorical data, respectively. Cox proportional hazards regression analyses were performed to determine hazard ratios (HRs) for incident GCA and 95% confidence intervals (CIs). The Wilcoxon matched-pair signed rank test was used for paired values in mutation segregation. The Benjamini-Hochberg correction was applied to multiple comparisons, and adjusted *P* values (*P*-adj) are noted. Odds ratios (ORs) for vision loss were assessed using Fisher's exact test and the Baptista-Pike method for CIs. The threshold

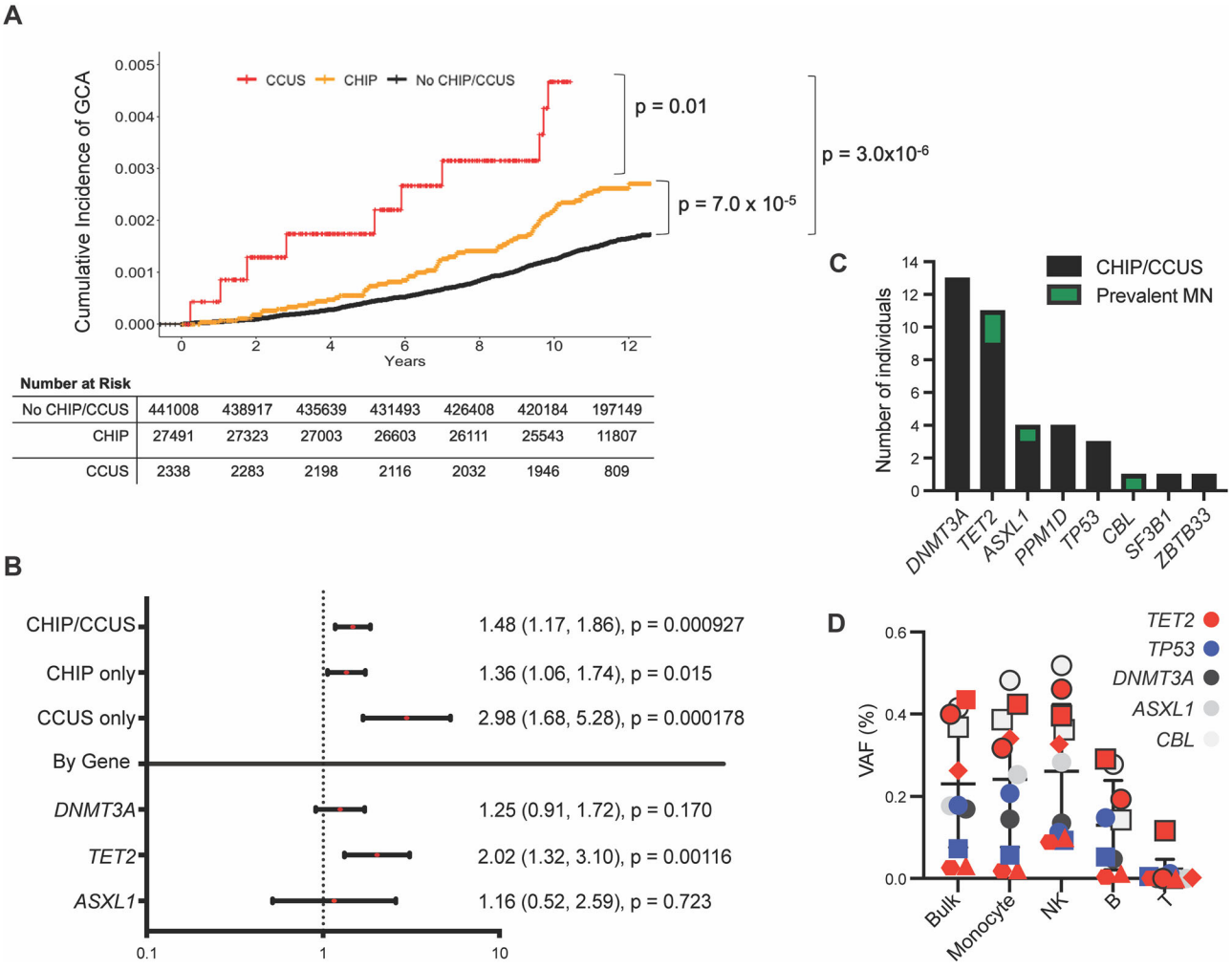

Figure 1. Genetic profile of CH in GCA cohorts. (A) Cumulative incidence of GCA in individuals with CCUS, CHIP, and no CHIP or CCUS. *P* values are determined by log-rank test. (B) Multivariable Cox proportional hazards model showing HRs for incident GCA among individuals from UKB with either CHIP or CCUS (CHIP/CCUS); CHIP popopulation only or CCUS population only; and *DNMT3A*, *TET2*, or *ASXL1*. In all cases, multivariable models were performed with the population without CHIP or CCUS (No CHIP/CCUS) as the reference group. Forest plot displays main effects (HR) with 95% CIs. Numerical values for HR (95% CI) with associated *P* values are provided to the right of each graph. (C, D) Characteristics of CH in individuals with GCA from MGB. (C) Stacked bar graph of individuals with mutations VAF ≥0.02 per gene. (D) VAF of mutations in sorted cells per cell type. Colors represent the mutated gene, and shapes represent distinct mutations per gene, with prevalent MN mutations outlined in black. Monocyte versus natural killer cell VAF: CH + MN *P*-adj = 0.2783, CH-only *P*-adj = 0.5781. Monocyte versus B cell VAF: CH + MN *P*-adj = 0.0059; CH-only *P*-adj = 0.0937. Monocyte versus T cell VAF: CH + MN *P*-adj = 0.0030, CH-only *P*-adj = 0.04680. CCUS, clonal cytopenia of uncertain significance; CH, clonal hematopoiesis; CHIP, clonal hematopoiesis of indeterminant potential; CI, confidence interval; GCA, giant cell arteritis; HR, hazard ratio; MGB, Massachusetts General Brigham; MN, myeloid neoplasm; *P*-adj, adjusted *P* value; UKB, UK Biobank; VAF, variant allele fraction.

for statistical significance was P/P-adj ≤ 0.05. For detailed methods, see Supplementary Methods.

RESULTS

CHIP and CCUS associated with incident GCA in the UKB. A total of 779 out of 470,960 (0.165%) individuals in the UKB had incident GCA. Of these, 82 individuals with incident GCA had CHIP or CCUS, and 697 did not (Supplementary Figure 1A). The cumulative incidence of GCA was significantly greater in those with CCUS ($P = 3.0 \times 10^{-6}$), CHIP ($P = 7.0 \times 10^{-5}$), and CHIP and CCUS populations combined ("CHIP/CCUS", $P = 6.0 \times 10^{-7}$) (Figure 1A, Supplementary Figure 1B). Multivariable Cox proportional hazards models adjusted for age, sex, and smoking history were performed to compare the risk of incident GCA in individuals with and without CHIP or CCUS. The HR for incident GCA was 1.48 (95% CI 1.17–1.856; $P = 0.000927$) in the CHIP/CCUS population relative to controls. The risk of incident GCA was 2.98-fold higher in CCUS ($P = 0.000178$) and 1.36-fold higher in CHIP ($P = 0.015$) relative to unmutated participants. Of the three most common CHIP and CCUS genotypes (*DNMT3A*, *TET2*, and *ASXL1*), *TET2* was the only genotype independently associated with increased risk for incident GCA (HR 2.02, 95% CI 1.32–3.10; $P = 0.00116$) (Figure 1B).

CHIP, CCUS, and MN prevalent in the MGB GCA cohort. We performed a genetic analysis of our cohort of 114 MGB patients with GCA, sequencing genes that are recurrently mutated in MN (Table 1). We detected these mutations in 31 individuals (27.2% of total cohort), including 28 (90.3%) who had CHIP or CCUS and 3 individuals (9.7%) with prevalent MN at GCA diagnosis (Supplementary Table 1). *DNMT3A*, *TET2*, and *ASXL1* mutations were the most common in the MGB cohort (Figure 1C). In four individuals with available PBMC samples (n = 3 CH, n = 1 MN), we flow sorted cells from different hematopoietic lineages and examined the VAF of mutations in each lineage. Mutations were detected in all cases in monocytes. Compared to monocytes, mutations were detected at equivalent VAF in natural killer (NK) cells and lower VAF in B cells, and they were rarely observed in T cells (Figure 1D).

Genotype-specific outcomes and GCA. We focused on vision loss because it is a severe, binary outcome in patients with GCA. We observed 19 vision loss events in 16 patients (Supplementary Figure 2A). We observed five cases of vision loss among individuals with either CHIP or CCUS and one case of vision loss in a patient with prevalent MN (Figure 2A, Supplementary Figure 2B). Of these six cases of vision loss and somatic mutations, four (66.6%) were in patients with biopsy-proven GCA with *TET2* mutations, and none were in patients with isolated *DNMT3A* mutations (Figure 2A, Supplementary Table 2). Evaluated by genotype, *TET2* mutations were significantly associated with vision loss (CH + MN: OR 4.33, 95% CI 1.25–17.8; $P = 0.047$; CH-only: OR 3.18, 95% CI 0.7971–12; $P = 0.134$; Figure 2B). C-reactive protein (CRP) was significantly lower in individuals who had somatic mutations and vision loss (CH + MN median CRP: 12.15 vs 122.0; $P = 0.0120$; CH-only median CRP: 13.9 vs 122.0; $P = 0.0190$; Figure 2C), whereas erythrocyte sedimentation rate was not different (Supplementary Figure 2B). Vision loss was commonly the event precipitating steroid initiation for suspected GCA (Supplementary Table 2, Supplementary Figure 2C). We observed that individuals with vision loss, before starting corticosteroids, had a lower lymphocyte relative and absolute counts (relative lymphocyte count: median 9.55% vs 18.15%; $P = 0.0042$; absolute lymphocyte count: median 1.03 vs 1.56; $P = 0.0023$; Figure 2D). The lower lymphocyte percentage among patients with GCA with vision loss was explained by a higher proportion of circulating myeloid cells, of which only the percentage of monocytes was significantly different (Supplementary Figure 2D–F). Hemoglobin and platelet counts were not different (Supplementary Figure 2G–H). Individuals with CHIP or CCUS and vision loss had larger clone sizes, measured by maximum VAF,

Table 1. Description of the confirmed MGB GCA cohort*

Patient characteristics	Total (n = 114)	No CHIP/CCUS (n = 83)	CHIP/CCUS (n = 28)	Prevalent MN (n = 3)
Age at GCA diagnosis, median (IQR)	73.2 (65.8–78.0)	73.0 (64.0–77.5)	75.5 (70.6–79.2)	82.9 (75.1–84.2)
Age at sequencing, median (IQR)	74.37 (67.5–80.3)	74.2 (65.8–78.5)	76.7 (70.4–81.7)	84 (76.8–84.8)
Years of follow-up, median (IQR)	5.75 (3.10–8.33)	5.7 (3.1–8.4)	6.0 (3.17–7.75)	3.08 (1.67–3.33)
Diagnosis type, n (%)				
Biopsy	65 (57)	45 (54.2)	17 (60.7)	3 (100)
Imaging	23 (20.2)	17 (20.5)	6 (21.4)	0 (0)
Clinical	26 (22.8)	21 (25.3)	5 (17.9)	0 (0)
Male sex, n (%)	31 (27.2)	18 (21.7)	11 (39.3)	2 (66.7)
Ever smoker, n (%)	50 (43.9)	37 (44.6)	12 (42.9)	1 (33.3)
PMR, n (%)	63 (55.3)	47 (56.6)	15 (53.6)	1 (33.3)
Vision loss, n (%)	16 (14.0)	10 (12)	5 (17.9)	1 (33.3)

* CCUS, clonal cytopenia of uncertain significance; CHIP, clonal hematopoiesis of indeterminate potential; GCA, giant cell arteritis; IQR, interquartile range; MGB, Massachusetts General Brigham; MN, myeloid neoplasia; PMR, polymyalgia rheumatica.

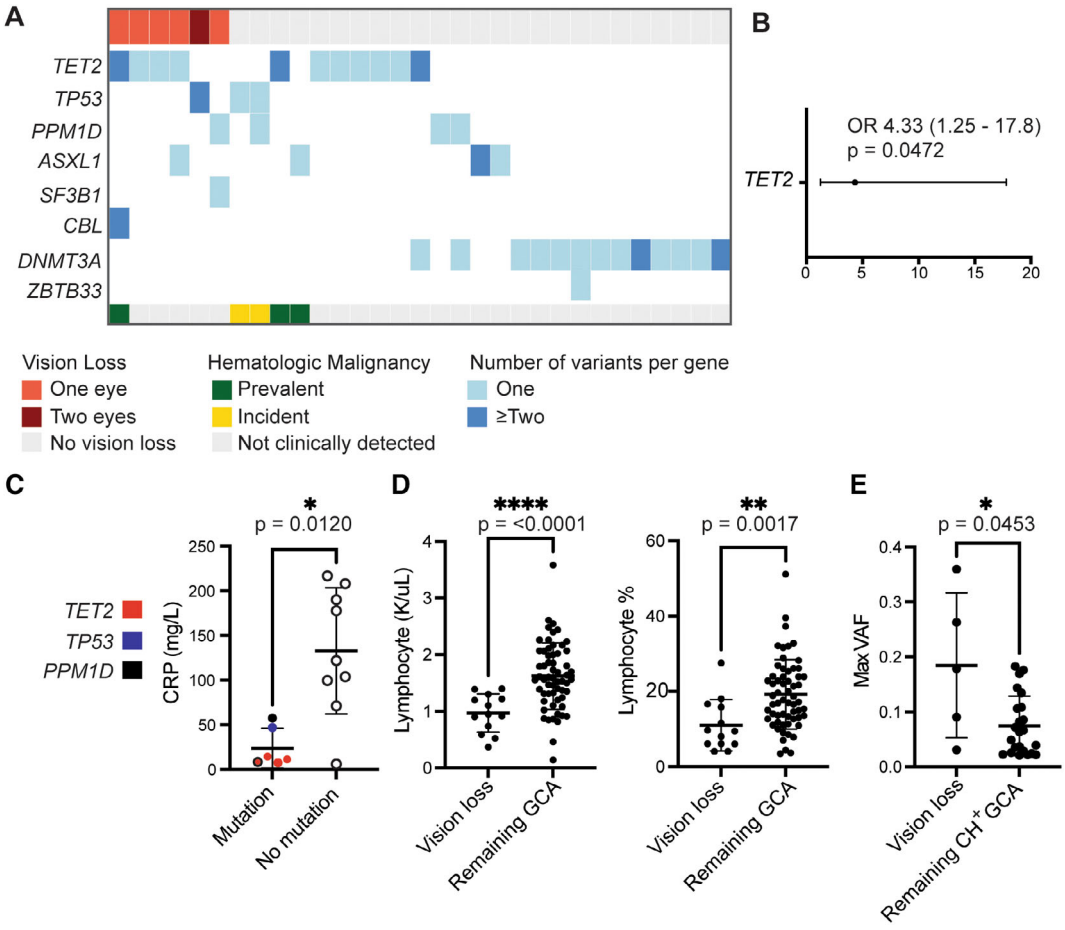

Figure 2. Clinical outcomes in patients with GCA with CH. (A) Co-occurrence matrix of severe outcomes in GCA clustered by outcome and genotype, where individuals are represented by one column. (B) Forest plot demonstrating OR for vision loss with *TET2* mutation across the MGB cohort. (C) Presteroid CRP in patients with GCA with vision loss with somatic mutation versus no mutation. (D) Presteroid lymphocyte percentage and absolute lymphocytes counts in patients with GCA with vision loss compared to those without vision loss, excluding prevalent MN. (E) Maximum VAF of individuals with CHIP or CCUS and vision loss compared to those without vision loss. CCUS, clonal cytopenia of uncertain significance; CH, clonal hematopoiesis; CHIP, clonal hematopoiesis of indeterminant potential; CRP, C-reactive protein; GCA, giant cell arteritis; MGB, Massachusetts General Brigham; MN, myeloid neoplasm; OR, odds ratio; VAF, variant allele fraction. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42738/abstract.

compared to those without vision loss (median max VAF 0.18 vs 0.0634; $P = 0.0453$; Figure 2E). We observed two cases of incident HM, both in patients with *TP53* mutations (Figure 2A, Supplementary Table 1).

Cytopenias, especially anemia, were common at diagnosis and at last follow-up, regardless of somatic mutation status (Supplementary Tables 3 and 4). A minority of patients with GCA were referred to hematology for cytopenia evaluation, and among those, an even smaller proportion underwent diagnostic evaluation for HM (Supplementary Table 5).

DISCUSSION

Here, we demonstrate an association between CHIP and incident GCA. More specifically, we find that incident GCA is more common in *TET2*-mutated CHIP and CCUS compared to other genotypes, and that *TET2* somatic mutations in aggregate, although not specifically in *TET2* CHIP and CCUS, are associated with GCA-related vision loss. Analysis of our institutional MGB cohort, although uncontrolled, is consistent with our findings in the UKB. Future prospective investigation of patients with GCA with CHIP, CCUS or MN with age- and sex-matched controls will allow for a more complete understanding of how mutations in myeloid driver genes influence clinical trajectories and adverse outcomes in this population.

GCA is predominantly a myeloid and $CD4^+$ T cell–mediated disease. In cases in which we examined the presence of somatic mutations in specific hematopoietic lineages, mutations were always present in monocytes but rarely detectable in T cells.[8,14] This suggests that the contribution of somatic mutation to GCA may be mediated by myeloid cells, as have emerged in the

mechanistic evaluation of a broad array of other *TET2*-associated conditions.[8] In other model systems, Tet2-deficient monocytes and macrophages display enhanced response to inflammatory stimuli, especially enriched for increased IL-1B and prolonged IL-6 production,[8–10,15,16] cytokines well recognized to be elevated in GCA monocytes.[2] More recently, increased proportions of dysregulated immature neutrophils have been described in a humanized mouse model of *TET2* CH, which have also been directly implicated in GCA pathogenesis through damage to the endothelium.[3,17] Our finding of reduced CRP in patients with somatic mutations and vision loss and reduced circulating lymphocytes in all individuals with vision loss, may similarly suggest cell intrinsic local activation of immune cells and expansion of myeloid cells, respectively, in GCA with adverse outcomes. The exact mechanisms by which *TET2* or other somatic variants may initiate vascular injury or lead to irreversible damage in GCA remains to be determined.

Features previously associated with increased risk of HM, namely, CCUS and larger clone size, were also associated with increased development of GCA and vision loss. Despite these associations, individuals from our institutional MGB cohort with GCA were not frequently evaluated for HM. We have recently shown that the risk of incident MN and all-cause mortality in CHIP and CCUS can be predicted with age; hematologic indices including mean corpuscular volume, red cell distribution width, and presence of cytopenia; and sequencing data regarding number, size, and type of genetic mutation.[7] This prognostication may be useful should genetic testing become more commonly used in GCA or other forms of vasculitis in the future. Moreover, as patients with CH are increasingly followed in designated clinics, clinicians should consider GCA in patients with *TET2* mutations and headache even in the absence of substantially elevated markers of inflammation.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ebert had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Robinette ML, DA Rao, PA Monach. The immunopathology of giant cell arteritis across disease spectra [review]. Front Immunol 2021;12:623716.
2. Wagner AD, JJ Goronzy, CM Weyand. Functional profile of tissue-infiltrating and circulating CD68+ cells in giant cell arteritis. Evidence for two components of the disease. J Clin Invest 1994;94(3):1134–1140.
3. Wang L, Ai Z, Khoyratty T, et al. ROS-producing immature neutrophils in giant cell arteritis are linked to vascular pathologies. JCI Insight 2020;5(20):e139163.
4. Roupie AL, Guedon A, Terrier B, et al. Vasculitis associated with myelodysplastic syndrome and chronic myelomonocytic leukemia: French multicenter case-control study. Semin Arthritis Rheum 2020;50(5):879–884.
5. Mekinian A, Grignano E, Braun T, et al. Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. Rheumatology (Oxford) 2016;55(2):291–300.
6. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms [review]. Leukemia 2022;36(7):1703–1719.
7. Weeks LD, Niroula A, Neuberg D, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. NEJM Evid 2023;2(5):EVIDoa2200310.
8. Belizaire, R, Wong WJ, Robinette ML, et al. Clonal haematopoiesis and dysregulation of the immune system [review]. Nat Rev Immunol 2023;23(9):595–610.
9. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med 2017;377(2):111–121.
10. Agrawal M, Niroula A, Cunin P, et al. TET2-mutant clonal hematopoiesis and risk of gout. Blood 2022;140(10):1094–1103.
11. Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis 2022;81(12):1647–1653.
12. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33(8):1122–1128.
13. Gibson CJ, Kim HT, Zhao L, et al. Donor clonal hematopoiesis and recipient outcomes after transplantation. J Clin Oncol 2022;40(2):189–201.
14. Arends CM, Galan-Sousa J, Hoyer K, et al. Hematopoietic lineage distribution and evolutionary dynamics of clonal hematopoiesis. Leukemia 2018;32(9):1908–1919.
15. Zhang Q, Zhao K, Shen Q, et al. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature 2015;525(7569):389–393.
16. Heimlich, JB, Bhat P, Parker AC, et al, Mutated cells mediate distinct inflammatory responses in clonal hematopoiesis. bioRxiv Preprint posted online December 5, 2022. doi: 2022.12.01.518580.
17. Huerga Encabo H, Aramburu IV, Garcia-Albornoz M, et al. Loss of TET2 in human hematopoietic stem cells alters the development and function of neutrophils. Cell Stem Cell 2023;30(6):781–799 e9.