Evaluation of the shared genetic component between giant cell arteritis and biomarkers of biological aging

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Introduction

Giant cell arteritis (GCA)

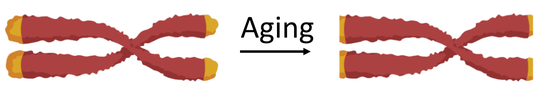
- Immune-mediated inflammatory disease which affects blood vessels
- **Complex etiology**: interplay between genetic and environmental factors

Aging is the strongest risk factor for GCA

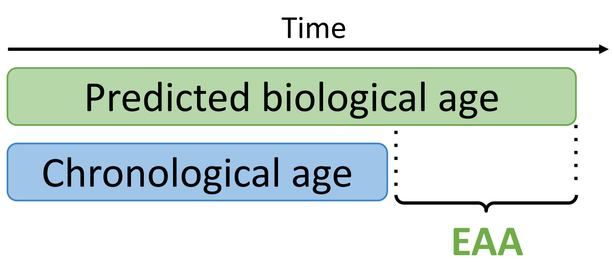
Biomarkers of biological aging

Leukocyte telomere length (LTL) and epigenetic age acceleration (EAA) are two markers of biological aging with a **complex etiology**

LTL



EAA



Biological age can be predicted by epigenetic clocks, based on DNA methylation alterations

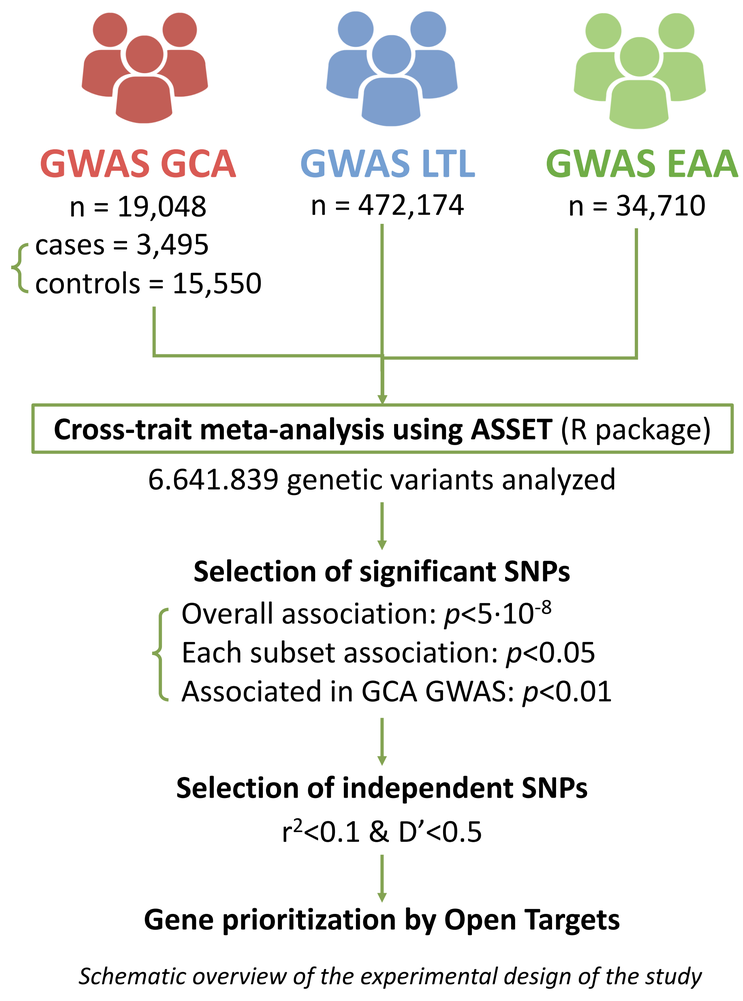
Hypothesis

Considering that advanced age represents a key factor for the development of GCA, we hypothesize that genetic factors influencing aging could also play a role in the development of this vasculitis

Objective

Explore the role of aging in GCA by analysing the shared genetic component between GCA and both markers of biological aging through a **cross-trait meta-analysis**

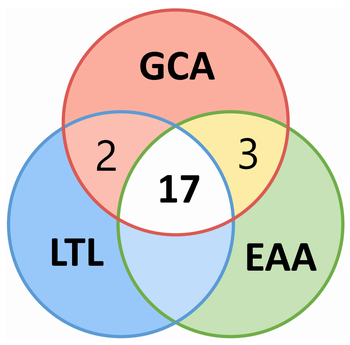
Materials & methods



Schematic overview of the experimental design of the study

Results & discussion

1 22 independent genetic variants were shared by GCA and at least one marker of aging, with 17 variants common to all three, indicating a **significant genetic overlap between GCA and the aging process**



Venn diagram illustrating the number of shared signals between GCA, LTL and/or EAA

Table 1. Results of the cross-trait meta-analysis and gene priorizitation

Region	Best subset meta	Best p-value meta	Prioritized gene Open Targets
1p13.2	GCA | TEL EAA	3,97E-14	*PTPN22*
			DCLRE1B
2p14	TEL EAA | GCA	1,29E-08	*SPRED2*
3q25.33	EAA | GCA TEL	4,23E-16	*SMC4*
4p16.3	GCA | TEL EAA	1,78E-14	*POLN*
			C4orf48
4q24	GCA | EAA	7,03E-10	*NFKB1*
			MANBA
5p15.33	TEL EAA | GCA	1,81E-30	*CLPTM1L*
			TERT
5q31.1	EAA | GCA TEL	5,39E-09	*JADE2*
5q31.1	GCA EAA | TEL	2,47E-09	*MACROH2A1*
			TIFAB
6q21	GCA TEL | EAA	1,26E-10	*CD164*
6q26	GCA EAA	2,43E-08	*PLG*
7q32.1	TEL EAA | GCA	1,16E-09	*IRF5*
8q12.1	TEL EAA | GCA	4,41E-09	*CHCHD7*
11q12.1	GCA EAA	1,20E-08	*SLC43A3*
			PRG2
12q13.13	GCA EAA | TEL	1,08E-08	*GPR84*
			NFE2
12q24.12	GCA TEL | EAA	3,92E-17	*SH2B3*
16p13.3	GCA EAA | TEL	9,98E-09	*TRAP1*
16q12.1	TEL| GCA EAA	2,68E-11	*HEATR3*
16q23.1	GCA | TEL	2,82E-14	*GLG1*
17p13.3	GCA | TEL EAA	4,03E-09	*SRR*
18p11.32	GCA TEL EAA	4,61E-10	*ENOSF1*
18q12.3	GCA TEL | EAA	3,41E-17	*SETBP1*
18q21.2	GCA TEL	2,71E-17	*POLI*

"|" separating traits in opposite directions

2 Genetic variants were prioritized to genes involved in **relevant pathways**

Immune response

PTPN22
NFKB1
IRF5

Clonal hematopoiesis

SETBP1
SH2B3
SPRED2

Telomere manteinance

DCLRE1B
TERT

Angiogenesis

PLG

3 Most of these variants act as eQTLs, **regulating gene expression levels**

Table 2. Functional annotation of shared genetic variants

	Blood eQTL	Immune cell eQTL	Vascular eQTL	Other tissue eQTL	pQTL	sQTL	CI
1p13.2_PTPN22	■	■		■			
1p13.2_DCLRE1B						■	
2p14_SPRED2	■			■		■	
3q25.33_SMC4		■		■		■	
4p16.3_POLN	■			■		■	
4p16.3_C4orf48				■			
4q24_NFKB1	■	■		■		■	■
4q24_MANBA	■	■		■	■		
5p15.33_CLPTM1L							■
5p15.33_TERT							
5q31.1_JADE2				■		■	
5q31.1_MACROH2A1							
5q31.1_TIFAB							
6q21_CD164	■			■			
6q26_PLG					■		
7q32.1_IRF5	■	■		■		■	
8q12.1_CHCHD7	■	■		■		■	
11q12.1_SLC43A3						■	■
11q12.1_PRG2						■	■
12q13.13_GPR84	■	■		■			
12q13.13_NFE2	■			■			
12q24.12_SH2B3	■			■			
16p13.3_TRAP1	■			■		■	
16q12.1_HEATR3	■	■	■	■		■	
16q23.1_GLG1							■
17p13.3_SRR	■	■	■	■		■	
18p11.32_ENOSF1	■	■		■		■	
18q12.3_SETBP1							
18q21.2_POLI	■	■		■			■

Funcional annotation data obtained from OpenTargets. **eQTL**, *expression quantitative trait loci;* ***pQTL****, protein quantitative trait loci;* ***sQTLs****, splicing quantitative trait loci;* ***CI****, chromatin interactions.*

Conclusions

This is the first study identifying a common genetic component between GCA and markers of biological aging.
Our finding represents a breakthrough in the understanding of the role of aging in the pathogenesis of this vasculitis.

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