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Matrix metalloproteinase-degraded type I collagen is associated with *APOE/TOMM40* variants and preclinical dementia

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Neurol Genet 2020;6:e508. doi:10.1212/NXG.0000000000000508

Abstract

Objective

Dysregulation of type I collagen metabolism has a great impact on human health. We have previously seen that matrix metalloproteinase–degraded type I collagen (C1M) is associated with early death and age-related pathologies. To dissect the biological impact of type I collagen dysregulation, we have performed a genome-wide screening of the genetic factors related to type I collagen turnover.

Methods

Patient registry data and genotypes have been collected for a total of 4,981 Danish post-menopausal women. Genome-wide association with serum levels of C1M was assessed and phenotype-genotype association analysis performed.

Results

Twenty-two genome-wide significant variants associated with C1M were identified in the *APOE-C1/TOMM40* gene cluster. The *APOE-C1/TOMM40* gene cluster is associated with hyperlipidemia and cognitive disorders, and we further found that C1M levels correlated with tau degradation markers and were decreased in women with preclinical cognitive impairment.

Conclusions

Our study provides elements for better understanding the role of the collagen metabolism in the onset of cognitive impairment.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

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Glossary

BMI = body mass index; **C1M** = MMP-degraded type I collagen; **CI** = confidence interval; ***CRP*** = C-reactive protein; **ECM** = extracellular matrix; **GWAS** = genome-wide association study; ***ICD-10*** = *International Classification of Diseases,* Tenth Revision; **MAF** = minor allele frequency; **MMP** = matrix metalloproteinase; **PERF** = Prospective Epidemiologic Risk Factor; **PCA** = principal component analysis; **PheWAS** = phenotype-genotype association analysis; **SNP** = single nucleotide polymorphism; **TAU-A** = ADAM10-degraded TAU; **TAU-C** = caspase-degraded TAU.

Many pathologies emerge after menopause, affecting the quality and duration of women's lives. Metabolic and endocrine changes occurring during the menopause transition have been linked with an increased incidence of chronic inflammatory and autoimmune disorders, in particular increased neuroinflammation.[1,2] A dysregulated extracellular matrix (ECM) metabolism is a common denominator in several age-related fibroproliferative pathologies and attributes to almost 45% of all deaths in the developed world.[3] Thus, improved preventive and predictive strategies for chronic fibroproliferative diseases could improve both quality of life and enhance longevity.

Type I collagens are among the most abundant extracellular matrix proteins in the body and are expressed in most connective tissues. During homeostasis, type I collagen is maintained in a delicate equilibrium between protein formation and degradation. Remodeling and repair of tissues is therefore essential for sustaining a healthy tissue or organ.[4] During the development of inflammatory diseases, the equilibrium between type I collagen formation and degradation is shifted, leading to an altered tissue remodeling and repair that in turn drives the disease.[5]

Blood-based biomarkers of collagen metabolism have been used as an alternative to classic tissue biopsy for prevention, diagnosis, and monitoring of patients. Accurate assessment of disease activity could allow measurable gain in the treatment time course.[6] We have developed a biomarker measuring serum levels of matrix metalloproteinase (MMP)-degraded type I collagen (C1M).[7] C1M is destroyed by cathepsin K, therefore making this a marker specific to soft tissue type I collagen. As MMPs are often are expressed by inflammatory cells, C1M reflects the remodeling potential of the body and cell inflammation. We have previously seen that C1M is associated with early death in postmenopausal women and with age-related pathologies such as fibrosis, cancer, and rheumatoid arthritis.[8–11]

Despite the enormous impact dysregulation of type I collagen metabolism has on human health, little is known about the genetic architecture of collagen metabolism. Greater insight into this topic could therefore help with the understanding of age-related pathologies.

In this study, we performed a genome-wide screen for association C1M in a population of 4,981 postmenopausal women from the Prospective Epidemiologic Risk Factor (PERF) study[12] using ca. 7.6 million genetic markers. Our objectives were to comprehensively identify genetic variants influencing the serum levels of C1M and test the relationship between identified genetic variants and common age-related pathologies and finally to investigate the role of collagen metabolism in these.

Methods

Study design

The PERF study was a follow-up study of Danish postmenopausal women aiming at identifying risk factors associated with age-related diseases.[12] A total of 5,855 women were enrolled at baseline (PERF I) between 1999 and 2001. Subjects in PERF have previously participated in clinical randomized placebo-controlled studies or were screened without being randomized for previous studies at the Center for Clinical and Basic Research. We performed a study inclusion process in 3 steps (figure e-1, links.lww.com/NXG/A317): we first collected subjects with demographic, serum, and blood biomarker measurements available with a missingness cutoff of less than 5%. Subjects without genotypes were excluded, and a study population level filter was applied on genotypes to remove cryptic relatedness.

Standard protocol approvals, registrations, and patient consents

The study was conducted in accordance with the International Conference on Harmonization–Guideline for Good Clinical Practice, and the study protocol was approved by the local ethics committees. All participants signed an informed consent, allowing future analysis to be performed.

Baseline measurements and data collection

At baseline, the subjects completed an interview with a doctor or a nurse covering questions related to physical health, demographics, lifestyle, and medical history. Fasting serum and DNA samples were collected from subjects who gave written consent for this specific analysis (n = 5,668 and n = 5,553, respectively).

C1M, caspase-degraded TAU (TAU-C) and ADAM10-degraded TAU (TAU-A) were measured blinded in serum by ELISA in a CAP-certified laboratory as previously described.[7,13,14] Lymphocyte and neutrophil counts were determined using an automated blood cell analyzer (Sysmex, Kobe, Japan). Serum cholesterol and triglycerides were

Table 1 Baseline characteristics of the PERF study

Variable	N	PERF study group
Baseline age, y, mean (SD)	4,891	70.1 (6.5)
Education, n	4,887	
Primary school		3,497
High school		1,044
University		346
Height, cm, mean (SD)	4,891	161.0 (5.9)
Weight, kg, mean (SD)	4,891	67.7 (11.6)
BMI, kg/m^2, mean (SD)	4,891	26.1 (4.2)
Systolic, mm Hg, mean (SD)	4,889	150.1 (24.3)
Diastolic, mm Hg, mean (SD)	4,891	81.8 (11.4)
Biochemistry, mean (SD)		
Total cholesterol: serum, mL	4,891	6.3 (1.1)
Triglycerides: serum, mL	4,891	1.4 (0.6)
LDL cholesterol: serum, ng/mL	1,002	3.5 (1.0)
HDL cholesterol: serum, ng/mL	2,896	1.7 (0.4)
Neutrophils count, 10e9/L	4,632	58.5 (8.9)
Lymphocyte count, 10e9/L	4,632	32.9 (8.1)
Biomarkers, mean (SD)		
C1M: serum, ng/mL	4,891	51.2 (47.9)
TAU-C: serum, ng/mL	4,885	22.0 (12.0)
TAU-A: serum, ng/mL	4,883	28.2 (16.1)
Cognitive tests		
SBT score, n	4,855	
0–9		4,684
10 or more		171
CFT score, n	4,851	
Over 14		4,333
14 or less		518
Lifestyle		
Smoking, n	4,891	
Never		2,306
Past		1,496
Current		1,089
Alcohol, n	4,871	
<7 alcohol units per week		3,271
>7 alcohol units per week		1,600

Abbreviations: BMI = body mass index; CFT = Category Fluency Test with animal naming; C1M = MMP-degraded type I collagen; MMP = matrix metalloproteinase; PERF = Prospective Epidemiologic Risk Factor; SBT = Short Blessed Test; TAU-A = ADAM10-degraded TAU; TAU-C = caspase-degraded TAU.
Characteristics of the subjects included in the study are shown (n = 4,981).

measured using the Advia 1800 analyzer (Siemens Healthcare Diagnostics, Munich, Germany).

Complete hospital disease history of the subjects was obtained for the period 1974–2014 by linking each individual's unique personal identification number (CPR number) with the Danish patient registries on December 31, 2014, corresponding to end of study. Subjects of the study were anonymized, and Central Personregister (CPR) numbers were not made available at any point of the study. Patient registry information was available for 5,602 subjects.

Disease phenotype definition

Fourteen disease phenotypes have been defined as all-time incidence of an event based on data available from multiple sources: biochemical marker levels, physiologic measurements, all-time incidence hospital records, death registry, questionnaire data from baseline consultation, on previous medical history at PERF I and PERF II enrollment times, and cognitive tests. The detailed list of included phenotypes and their inclusion criteria is provided in table e-2 (links.lww.com/NXG/A317). In this study, dementia was defined as (1) *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes F01-F03 G31-G32, (2) The Short Blessed Test ≥10 and the Category Fluency Test ≤14, or (3) dementia noted in questionnaires. Alzheimer disease was defined as (1) *ICD-10* codes F00+G30 or (2) Alzheimer disease noted in questionnaires.

Genotyping and imputation

Of 5,553 DNA samples collected, 5,516 have been genotyped successfully. Genotyping was performed using a custom-made Illumina Global Screening Array (693,143 probes) in collaboration with deCODE Genetics, Iceland. Single nucleotide polymorphism (SNP) imputation was performed using the Michigan Imputation Server.[15] The reference panel used for this step is the HRC r1.1.2016, EUR population. Phasing was performed with ShapeIt2 and the imputation with Minimac3. Using a curated set of 563,532 probes, we imputed 39131581 positions. Positions are reported as in the GRCh37 reference.

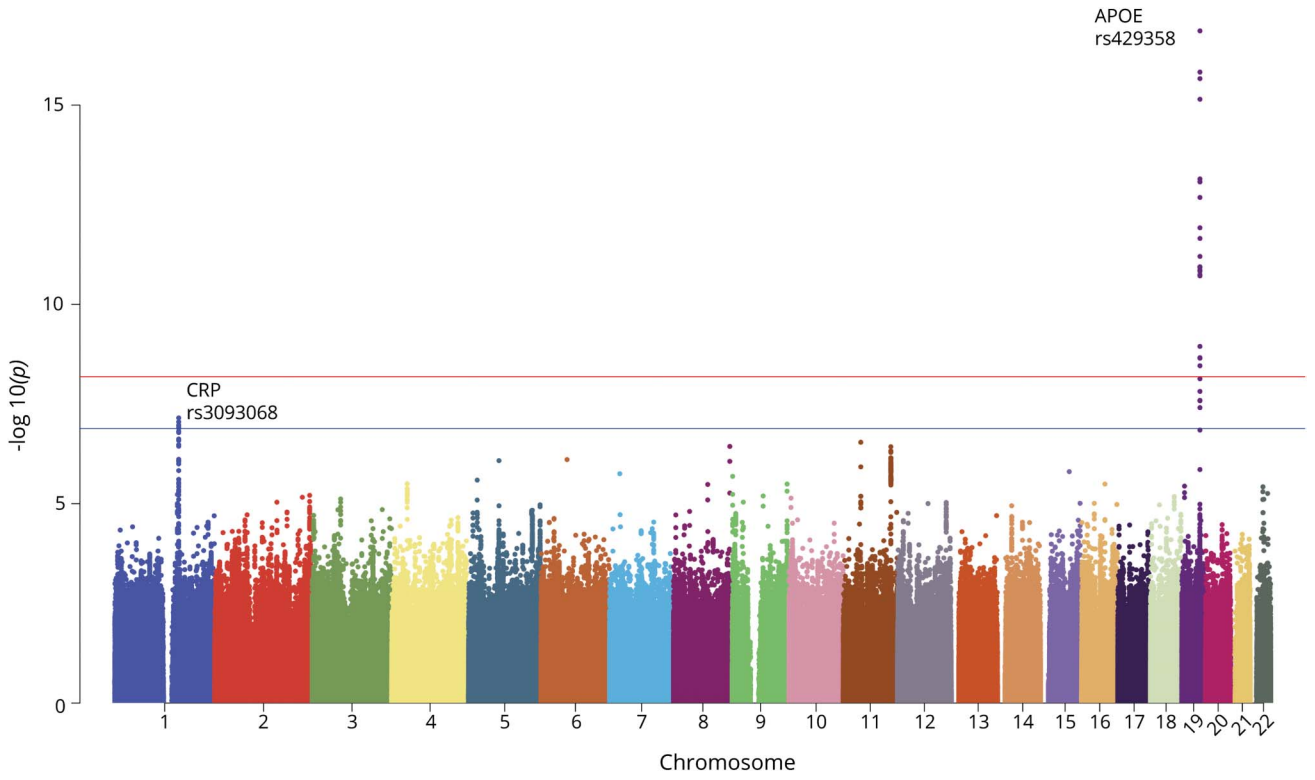
Probe-level filtering

Standard probe-level filtering has been performed using a minimum probe call rate of 97%, a minor allele frequency (MAF) greater than or equal to 1%, and a Hardy-Weinberg equilibrium *p* value cutoff greater than or equal to 1e-6. No filtering on multiallelic SNPs has been performed. In total, 534,710 probes and 7,672,338 imputed positions were tested in the association screening, respectively.

Individual-level filtering

To address possible cryptic relatedness between subjects, we calculated an identity-by-descent coefficient using Plink[16] –genome function. Inbreeding coefficient was calculated using the plink –ibc function. We removed patients, on a 1 side of a pair basis, using a minimum *PI_HAT* cutoff value of 0.1875, and a cutoff of less than −0.1 or greater than 0.1 was

Figure 1 Single nucleotide polymorphisms associated with log2 levels of type I collagen metabolite in serum



Genome-wide and suggestive significance thresholds have been revised according to the number of tests (6.5e-9 and 1.3e-7, respectively) and are indicated by the red and blue lines. CRP = C-reactive protein.

applied to the *Fhat2* coefficient. In total, 136 of 5,516 individuals have been removed in this step.

Principal component analysis

Population-based genetic variation in the data set was captured using EIGENSTRAT Smartpca 7.2.0[17,18] to perform an iterative principal component analysis (PCA) of the study population with available genotypes (n = 5,106) on the nonimputed filtered variants using the default parameters. The scree plot of the first 10 components and the PCA plot of the 2 leading components are shown in figures e-6 and e-7 (links.lww.com/NXG/A317). The first 3 components capture the largest share of explained variance (0.3%).

Linear regression

Linear additive regression was performed on the genome-wide association study (GWAS) population (n = 4,981) to identify genetic associations with log2-transformed serum C1M levels using plink v1.90p adjusted for baseline age, body mass index (BMI), and the 3 leading principal components, and prebaseline occurrence of cancer, inflammatory arthropathies, and spondylopathies, defined as events up to 1 year after baseline to address potential influence on C1M levels. The plink switches –allow-no-sex and –keep-allele-order were also used. Subjects with missing biomarker levels were not included in the analysis. Conservative significance thresholds based on the number of screened variants were defined as equal to 6.5e-9, i.e., 0.05/N, and 1.3e-7, i.e., 1/N, N = 7672,338, for the genome-wide and suggestive values, respectively. The Manhattan plot visualization has been made using the R package qqman[19] and color palette from ggsci.

Phenotype-genotype association analysis

Phenotype-genotype association analysis (PheWAS) was performed using a logistic regression model, corrected for baseline age, BMI, and the 3 leading principal components. The *Z*-statistic of the regression was reported and visualized with a heatmap, generated by the R package ComplexHeatmap.[20]

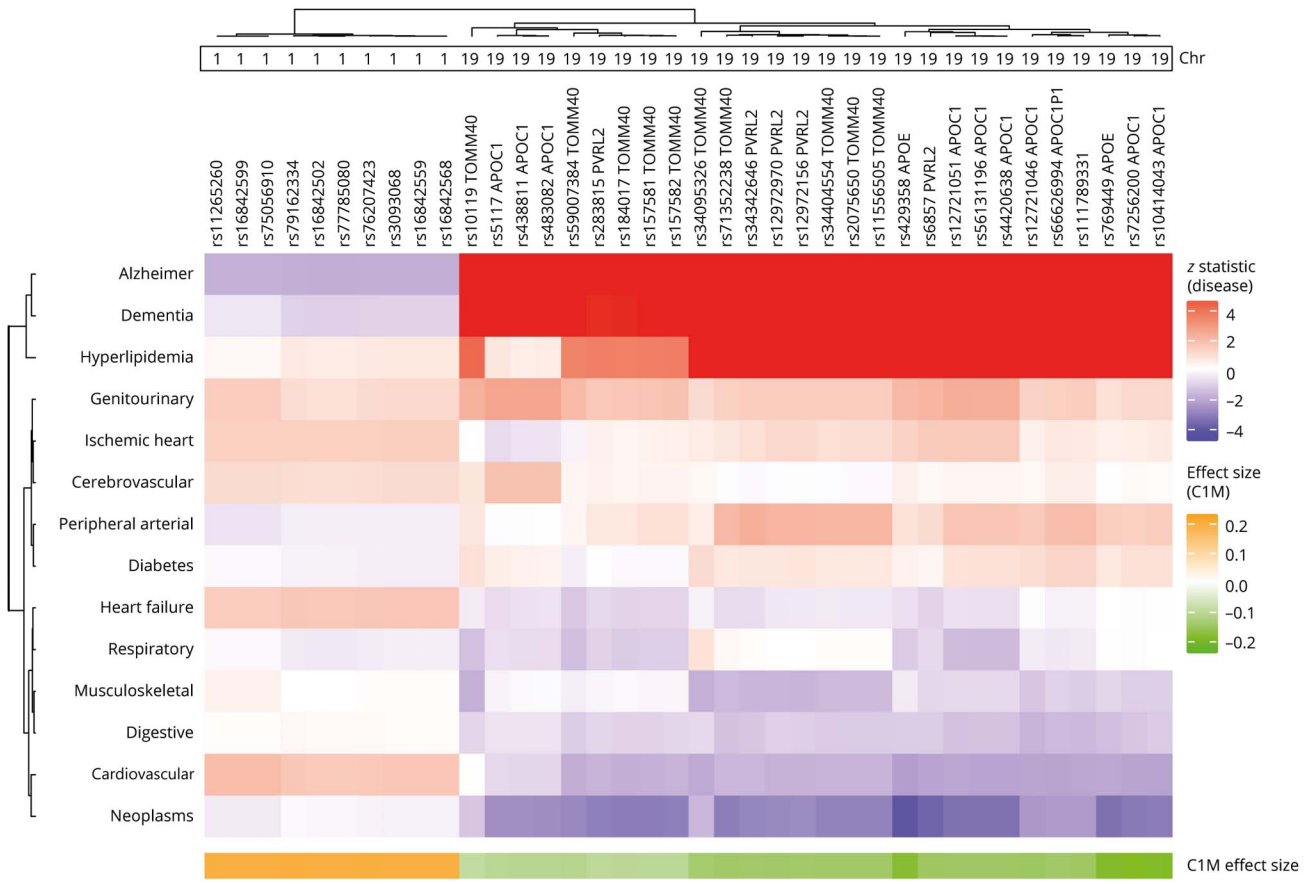
Biomarker boxplot visualization

Serum and blood biomarker level distributions across time to occurrence of Alzheimer disease relative to baseline were shown using R ggplot2 functions. Tests of biomarker distributions between time intervals were performed using an analysis of variance on log-transformed values with post hoc comparisons with the Holm-Sidak multiple comparisons test.

Data availability

The original data of the PERF study and the linkage data from various health registries are currently stored at Nordic Bioscience. Access to this database will be granted, on condition that researchers have appropriate ethical permission and sign the appropriate Material Transfer Agreement form.

Figure 2 Phenotype-genotype association analysis of the 38 genetic variants identified by the GWAS



The effect sizes of the genetic association with type I collagen degradation marker (C1M) are shown in orange/green. *Z*-statistics of the phenotype/genotype association analysis are shown on the heatmap in red/blue. GWAS = genome-wide association study.

Results

Study design

A total of 5,855 subjects have been included in the PERF study at baseline. For a majority of these, genotyping (n = 5,516) has been performed, and serum and blood biomarkers (n = 5,668) were measured. More details are available in the Material and Methods section and in the cohort profile presentation paper.[12] A GWAS was performed on the maximum population with both genotypes, demographic and biomarker measurements, and data availability from the Danish patient registries (n = 4,891). Table 1 summarizes the baseline characteristics of the study group.

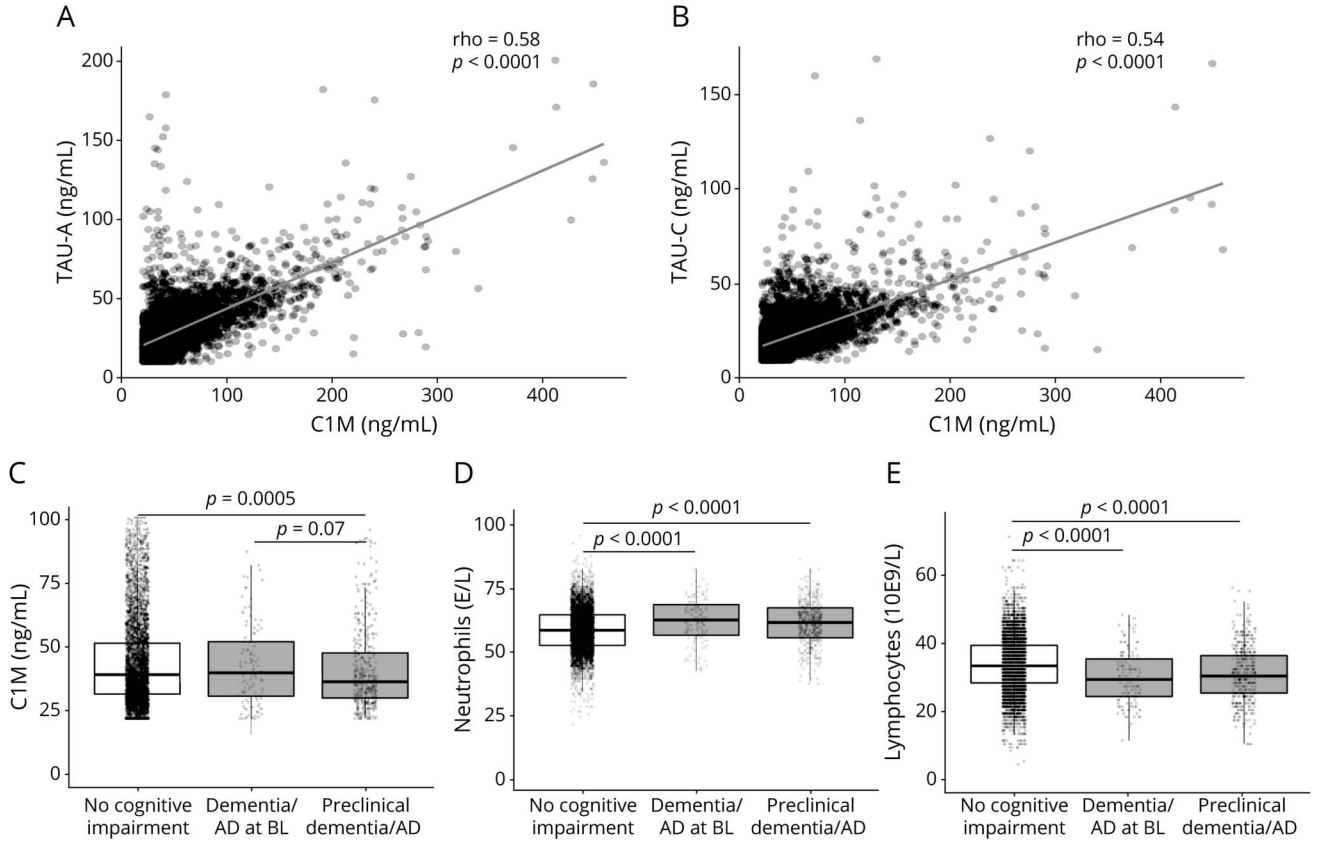
Genetic associations with C1M levels

We identified 22 genome-wide significant SNPs associated with C1M, located primarily in the chr19q13.32 *APOE-C1/TOMM40* gene locus (figure 1 and table e-1, links.lww.com/NXG/A317). Within this cluster, the most significant association with *APOE* variants was rs429358—located in exon 4, and which combination with rs7412 is commonly known as *APOE* ε4 (p = 1.38e-17, effect size: −0.162; 95% confidence interval [CI] −0.199 to −0.1248 log2 ng/mL per additional minor allele) and rs769449 (p = 7.15e-16, effect size: −0.166; 95% CI −0.209 to −0.129 log2 ng/mL). Nine genetic variants near the *APOC1* gene were significantly associated with C1M including rs4420638 (p = 8.44e-14) and 4 associations with *PVRL2* variants including rs6857 (p = 2.07e-13). SNPs in this locus are relatively common (MAF from 0.13 to 0.25) and in moderate linkage disequilibrium, see figures e-2 and e-4 for the LD structure and the locus plot of the region. An additional 6 suggestive associations were found in this locus, centered around *TOMM40*. All genome-wide significant associations in chr19 had a negative effect size (β-coefficients ranging −0.108 to −0.169 log2 ng/mL). We identified 10 suggestive associations near the gene C-reactive protein (*CRP*), mostly located downstream (locus plot shown in figure e-3). The nearest associated variant was rs3093068 (p = 1.09e-7) with a positive effect (β = 0.172; 95% CI 0.108–0.235 log2 ng/mL).

Phenotype-genotype association analysis

A PheWAS was performed on the 38 SNPs screened by the GWAS (figure 2 and table e-5, links.lww.com/NXG/A317). The variants identified in *APOE-C1/TOMM40* cluster were positively associated with the incidence of dementia and Alzheimer disease (*Z*-statistic range 4.89–9.47) as well as

Figure 3 Association of C1M with tau degradation biomarkers (TAU-A and TAU-C) and preclinical dementia and Alzheimer disease



(A) Dot plot of TAU-A and C1M in PERF. The rho value is calculated with Spearman correlation. (B) Dot plot of TAU-C and C1M in PERF. The rho value is calculated with Spearman correlation. (C) Box plot showing C1M levels in women with no cognitive impairment (never diagnosed with dementia/Alzheimer disease), women diagnosed with dementia/Alzheimer disease at baseline (diagnosed up to 2 years after baseline), and women with preclinical dementia/Alzheimer disease (diagnosed with dementia or Alzheimer disease more than 2 years after baseline). (D and E) Neutrophils and lymphocytes levels in women with no cognitive impairment (never diagnosed with dementia/Alzheimer disease), women diagnosed with dementia/Alzheimer disease at baseline (diagnosed up to 2 years after baseline), and women with preclinical dementia/Alzheimer disease (diagnosed with dementia or Alzheimer disease more than 2 years after baseline). Statistical assessment was performed using a Wilcoxon test. C1M = MMP-degraded type I collagen; MMP = matrix metalloproteinase; PERF = Prospective Epidemiologic Risk Factor; TAU-A = ADAM10-degraded TAU; TAU-C = caspase-degraded TAU.

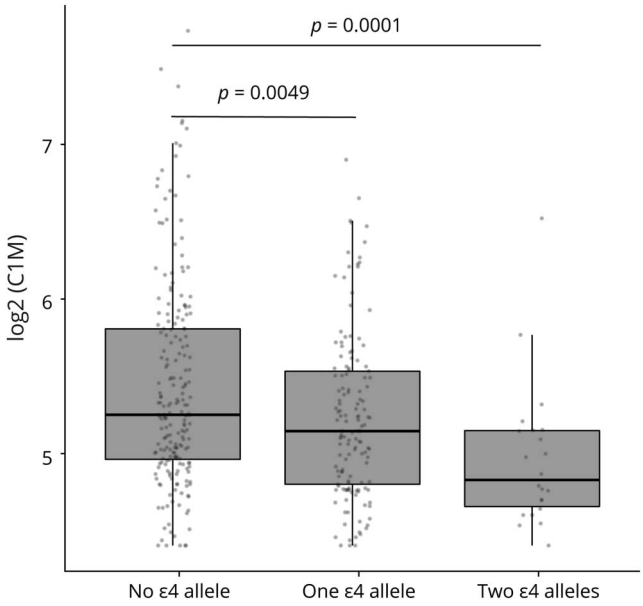
hyperlipidemia (*Z*-statistic range 3.06–6.32). It was previously shown that rs429358 was associated with the increased serum total cholesterol level and depression severity, and the authors hypothesized *APOE* variants to be detrimental to recovery of nerve function after stroke.[21] By performing a GWAS, corrected for BMI, baseline age, and population structure, we confirmed that *APOE* variants were associated with total cholesterol, with top hit rs7412, $p = 3.4e\text{-}47$ (figure e-5). Functional analyses (table e-6) showed an enrichment of GO terms related to regulation of cholesterol biosynthetic process, lipoprotein particle receptor binding, protein-lipid complex binding, and low-density lipoprotein particle remodeling. In addition, these variants were associated with decreased incidence of neoplasms (*Z*-statistic range −3.04 to −2.12).

Variants located in the chr1 *CRP* gene locus had a weak association with cardiovascular traits (*Z*-statistic range 1.33–1.67) and a negative association with dementia and Alzheimer disease.

C1M degradation in preclinical dementia/Alzheimer disease

We have previously shown that biomarkers of ADAM10- and caspase-degraded tau (TAU-A and TAU-C) were negatively associated with dementia in PERF.[22] In the current study, we noted that there was a strong correlation between C1M and tau degradation biomarker levels ($r = 0.54$ between TAU-C and C1M, $r = 0.58$ between TAU-A and C1M, figure 3, A and B). By grouping dementia/Alzheimer disease incidences into 2 bins: (1) dementia/Alzheimer disease at baseline (diagnosed less than 2 years after baseline) and (2) preclinical dementia/Alzheimer disease (diagnosed more than 2 years after baseline), and looking at C1M levels, we observed that women with preclinical dementia/Alzheimer disease had lower levels of C1M compared with women with dementia/Alzheimer disease at baseline and women with no cognitive impairment (never diagnosed with dementia/Alzheimer disease, figure 3C). We also found that women diagnosed with both dementia/Alzheimer disease at baseline and preclinical

Figure 4 C1M degradation biomarkers stratified by *APOE* e4 genotype in preclinical dementia/Alzheimer disease



Log2-transformed C1M biomarker levels (ng/mL) in subjects with preclinical dementia/Alzheimer disease defined as in table e-2 (links.lww.com/NXG/A317) are shown according to their APOE e4 genotypes. Statistical assessment of C1M levels between no APOE e4 allele carriers and *APOE* e4 allele carriers was performed using a Wilcoxon test. C1M = MMP-degraded type I collagen; MMP = matrix metalloproteinase.

dementia/Alzheimer disease had lower levels of neutrophils and higher levels of lymphocytes compared with women with no cognitive impairment (figure 3, D and E).

C1M degradation stratified by *APOE* ε4 genotype in preclinical dementia/ Alzheimer disease

We looked at the C1M degradation biomarker levels in the subpopulation of women with preclinical dementia/ Alzheimer disease (n = 370), stratified by their *APOE* ε4 genotypes, obtained from the 2 variants rs429358 and rs7412 (figure 4). We see an allele dose effect between women with no *APOE* ε4 allele and women carrying 1 and 2 *APOE* ε4 alleles (1-sided Wilcoxon test $p < 0.0001$). This result, in line with the GWAS, further demonstrates the negative association between *APOE* genotypes and C1M in preclinical dementia/Alzheimer disease.

Discussion

We investigated the genetic component in the variation of C1M in a population of postmenopausal Danish women. This biomarker reflecting inflammation and remodeling potential of the body has been previously described to be associated with age-related diseases such as cancer, fibrosis, and rheumatoid arthritis.[8–11] The aim of our study was to systematically discover genetic factors of variation of C1M and link these variants to age-related diseases. The PERF cohort offered an ideal exploratory environment combining single nucleotide variants, demographic, and electronic hospital care history.

Genome-wide association analysis of C1M levels in our study population identified two main genomic regions: chr19 q13.32 *APOE-C1/TOMM40* cluster and chr1q23.3, which encompasses the gene *CRP*. SNPs in the *APOE* cluster were dominantly associated with lower C1M levels, whereas SNPs within *CRP* were associated with a higher C1M level. Power calculations performed using a type I error cutoff at 5e-8 showed that the association found in the *APOE* locus was sufficiently supported (statistical power for rs429358: 0.68) while findings within *CRP* would require a larger sample size.

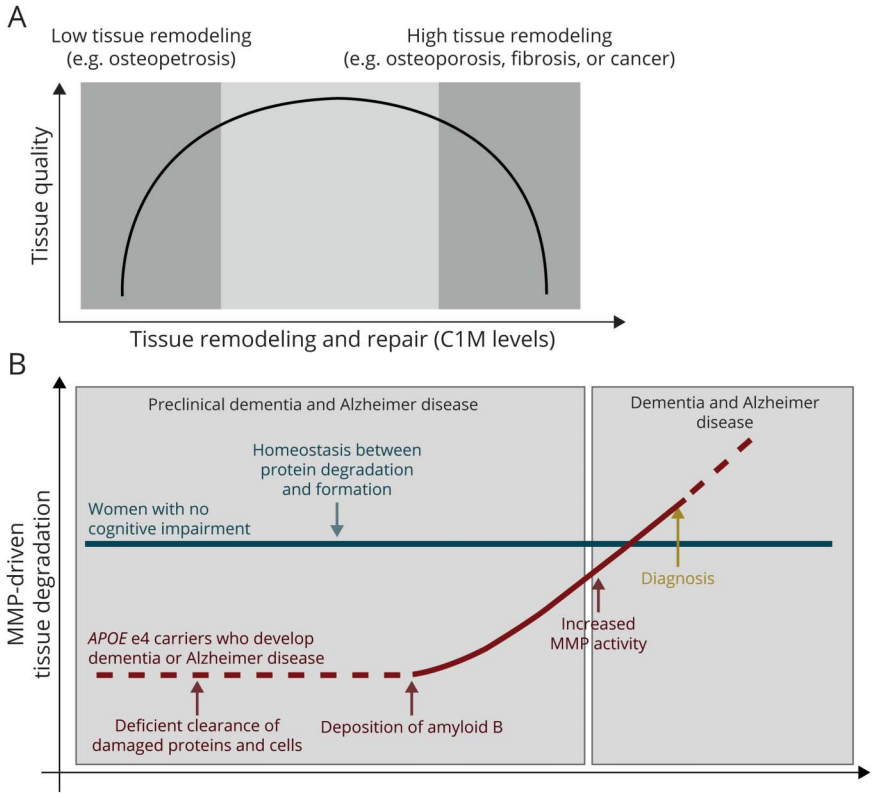
Although our PheWAS analysis did not identify strong associations with SNPs within the *CRP* gene locus, except for a few markers previously associated with heart disease, we found that the variants associated with C1M in the *APOE-C1/TOMM40* locus were strongly associated with dementia and Alzheimer disease, as for example, the well-studied variant rs429358, which is a risk factor for neural regeneration in late-onset Alzheimer disease.[23–25]

The analysis of *APOE* ε4 genotype frequencies (rs429358 and rs7412) in our study population (tables e-3 and e-4, links.lww.com/NXG/A317) showed that they were in agreement with those observed in the Danish general population[26] and that *APOE* ε4 genotypes were overrepresented in the individuals with Alzheimer disease (χ^2 test $p = 3.6e\text{-}16$). To further study the link between type I collagen remodeling and in preclinical dementia/Alzheimer disease, we showed that C1M levels could be stratified by their *APOE* ε4 genotypes, with significantly lower C1M levels in *APOE* ε4 double carriers compared with subjects without ε4 alleles.

When we looked further into the biomarker dynamics in subjects with cognitive impairment, we found that C1M correlated with tau degradation markers (TAU-A and TAU-C). We have previously seen that high levels of the tau degradation markers were associated with a lower risk of preclinical dementia and Alzheimer disease.[22] A plausible explanation for this could be linked to microglial activation. In early stages of dementia and Alzheimer disease, microglial activation is believed to be neuroprotective by enhancing phagocytosis and degradation of β-amyloid and tau,[27,28] a process that may result in less release of tau degradation products to the periphery. In later stages, where microglia become overactivated, they lose their phagocytic abilities, resulting in uncontrolled inflammation releasing degraded tau to the periphery.[29]

In this study, C1M levels were also lower in subjects with preclinical dementia/Alzheimer disease compared with subjects diagnosed close to baseline and subjects with no cognitive impairment. We hypothesize that *APOE* ε4 carriers are born with a low remodeling potential (low C1M levels), which increases the risk of dementia/Alzheimer disease along with other age-related diseases because of inefficient clearance of damaged proteins and cells (figure 5B). In subjects with low

Figure 5 MMP degradation and tissue remodeling across disease progression



(A) The U-shaped curve of the relationship between tissue remodeling and repair (C1M levels) and tissue quality and in turn the risk of developing age-related diseases. (B) Hypothesis drawing showing the levels of MMP-driven tissue degradation during the progression of dementia/Alzheimer disease and in subjects with no cognitive impairment. C1M = MMP-degraded type I collagen; MMP = matrix metalloproteinase.

remodeling potential, the clearance of amyloid-β will be inefficient, leading to formation of amyloid-β oligomers and plaques. This will in turn initiate chronic inflammatory processes and thereby increase C1M levels in the later stages of the disease (figure 5A).

We also found that women with either dementia/Alzheimer disease baseline or preclinical dementia/Alzheimer disease had increased neutrophil count and decreased lymphocyte count compared with subjects with no cognitive impairment. It is well known that chronic inflammation worsen during the course of dementia and Alzheimer disease.[2,30–32] Proinflammatory cytokines have been detected in the periphery, indicating that a strong innate immune response is occurring throughout disease progression and triggered by the dysregulation of the Aβ peptide.[33] A decreased lymphocyte count have on the other hand been shown lead to greater accumulation of amyloid Aβ plaques and microglia activation in mice,[34] indicating that the adaptive immune system is dysfunctional in subjects with Alzheimer disease.

Together, the results of this study suggest that targeting inflammation or the remodeling potential could be relevant for therapeutic interventions and preventive strategies; however, the study population should be stratified according to parameters including *APOE* genotype and inflammatory phenotype.

There are a few potential limitations in our study. Type I collagen is ubiquitous and may be affected by external factors. We addressed this by correcting for disease conditions previously associated with elevated C1M levels. Medications could also potentially modulate type I collagen remodeling. Use of medication was available as survey information for a part of the follow-up group (n = 1,856). Sensitivity analysis performed for frequently reported medications, e.g., estradiol and paracetamol, showed that the effect sizes of the reported SNPs did not deviate more than 1.5%, and therefore, medication could be disregarded from the GWAS model. Neuropathologic confirmation was not available for this study. Diagnosis was based on a combination of data from the Danish national patient registry, questionnaires, and cognitive tests (table e-2, links.lww.com/NXG/A317). Finally, gene expression was not collected in the PERF study. Evaluating the impact of genetic variants on gene expression could contribute to better understand the impact of type I collagen remodeling in cognitive disorders.

In conclusion, our study uncovers the link of type I collagen remodeling in lipoprotein balance and onset of dementia and Alzheimer disease. Our results suggest that blood-based measurements of inflammation and tissue remodeling could be relevant as a first-line therapeutic intervention.

Acknowledgment

The authors thank Unnur Styrkársdóttir for her valuable help in the genotyping of the PERF samples and insightful discussions; Line Mærsk Staunstrup for her contribution to the PERF database curation; and Peder Frederiksen for valuable scientific discussion.

Study funding

J.P.M. Blair was funded by a PhD grant from the Danish Research Foundation.

Disclosure

M.-H.E. Tang and C.L. Bager are employed at ProScion. A.-C. Bay-Jensen, K. Henriksen, and M.A. Karsdal are employed at Nordic Bioscience. A.-C. Bay-Jensen, C. Christiansen, and M.A. Karsdal hold stocks in Nordic Bioscience. No other potential conflicts of interest relevant to this article were reported. Go to Neurology.org/NG for full disclosures.

Publication history

Received by *Neurology: Genetics* May 13, 2020. Accepted in final form July 28, 2020.

Appendix Authors

Name	Location	Contribution
Man-Hung Eric Tang, PhD	ProScion, Herlev, Denmark	Designed and conceptualized the study; analyzed and interpreted the data; and drafted the manuscript for intellectual content
Joseph P.M. Blair, MSc	ProScion, Herlev, Denmark	Analyzed and interpreted the data and revised the manuscript for intellectual content
Cecilie Liv Bager, PhD	ProScion, Herlev, Denmark	Major role in the acquisition of data; interpreted the data; and drafted the manuscript for intellectual content
Anne-Christine Bay-Jensen, PhD	Nordic Bioscience, Herlev, Denmark	Interpreted the data and revised the manuscript for intellectual content
Kim Henriksen, PhD	Nordic Bioscience, Herlev, Denmark	Interpreted the data and revised the manuscript for intellectual content
Claus Christiansen, MD	Nordic Bioscience, Herlev, Denmark	Major role in the acquisition of data and revised the manuscript for intellectual content
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