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A TGF-β1 polymorphism association with dementia and neuropathologies: The HAAS

Rita Peila [a,b,*,1,2], Berran Yucesoy [c,3], Lon R. White [b,d,2,4], Victor Johnson [c,3], Michael L. Kashon [e,5], Kim Wu [a,1], Helen Petrovitch [b,2], Michael Luster [c,3], Lenore J. Launer [a,1]

[a] *Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, National Institutes of Health, 7201 Wisconsin Avenue, Suite 3C-309, Bethesda, 20892-9205 MD, USA*

[b] *Pacific Health Research Institute, 846 South Hotel Street, Suite 307, Honolulu, HI 96813, USA*

[c] *Toxicology and Molecular Biology Branch, National Institute for Occupational Safety and Health, USA*

[d] *Department of Geriatric Medicine, John A Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, USA*

[e] *Biostatistic Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV, USA*

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Abstract

The transforming growth factor-β1 (TGF-β1) is involved in post-ischemic neuronal rescue and in β-amyloid turn-over. We hypothesized that the risk for dementia and related neuropathologies is modified by the TGF-β1 functional genetic variants. The association of the TGF-β1 + 29T → C polymorphism with dementia was examined in a sample of 261 cases and 491 controls from the Honolulu-Asia Aging Study, including 282 subjects with autopsy data. Dementia was assessed in 1991 and 1994 by a multi-step protocol and standardized diagnostic criteria. The analysis was adjusted for demographic and vascular factors. Compared to the TT genotype, the TC and the CC genotypes were associated with a reduced risk for vascular dementia ($OR_{TC} = 0.28$, 95% confidence interval (CI): 0.1–0.9; $OR_{CC} = 0.28$, CI: 0.1–0.9), microinfarcts ($OR_{CC} = 0.31$, CI: 0.13–0.71) and cerebral amyloid angiopathy ($OR_{CC} = 0.48$, CI: 0.2–0.9). The CC genotype was associated with an increase risk of neocortical plaques ($OR_{CC} = 4.34$, CI: 1.6–11.8). These preliminary data suggest that the TGF genetic variability may be important in the risk of vascular related dementia.

Keywords: Transforming growth factor-β1; Dementia; Cerebral microinfarcts

1. Introduction

The transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine expressed by several cellular types in the periphery, and by glia and neurons in the brain. In experimental studies TGF-β1 mRNA expression and protein production increase dramatically after a cerebral ischemic event [28]. TGF-β1 appears to protect the area surrounding the ischemic region by maintaining neuronal viability and function through an interaction with microglia and astrocyte metabolism [6,9]. In contrast to its neuroprotective properties on ischemic events, TGF-β1 has also been implicated in the neurotoxic events associated with the Alzheimer's disease amyloid cascade (AD) [38], however the exact role of TGF-β1 in this process is under investigation.

TGF-β1 protein level is predominantly under genetic control and some of the polymorphic variants affect the protein level [7]. The T → C single nucleotide polymorphism (SNP) at nucleotide 29 of the TGF-β1 signal sequence causes

* Corresponding author. Tel.: +1 301 496 6292; fax: +1 301 496 4006.
E-mail address: peilar@mail.nih.gov (R. Peila).
[1] Tel.: 1 301 496 1178.
[2] Tel.: 1 808 564 5420.
[3] Tel.: 1 304 285 5993.
[4] Tel.: 1 808 564 5421.
[5] Tel.: 1 304 285 6209.

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a leucine → proline substitution at codon 10 of the amino acid sequence [2]. The C allele (mutant allele) of this polymorphism has been associated with a higher level of TGF-β1 mRNA and protein compared to the wild-type T allele [30,40]. The C allele has also been associated with a reduced risk for myocardial infarction, rheumatoid arthritis and osteoporosis [29,39,40]. The T allele of the −509C → T SNP located in the promoter region has been associated with a modest increased risk for AD and with a slightly higher transcriptional activity compared to the C allele [20].

Based on these observations we hypothesized that the TGF-β1 allelic variants could modulate the occurrence of vascular-related dementia (VaD) by reducing ischemic damage. This study was therefore designed to examine the association of TGF genetic variants with the risk of the two most common types of dementia (AD and VaD) and related neuropathologies. The study is based on a sample drown from the Honolulu-Asia Aging Study (HAAS), a community-based longitudinal study.

2. Methods

2.1. Study population

The HAAS is a follow-up of the Honolulu Heart Program (HHP), a longitudinal community-based study of coronary heart disease and stroke in Japanese-American men born between 1900 and 1919 and living in Oahu, Hawaii in 1965 when the study begun [31]. The baseline HHP exam was followed by two additional exams in 1967–1970 and 1971–1974. At each exam, data were collected on sociodemographic and health related factors. In 1991 the HAAS was established to study neurodegenerative diseases [35]. A total of 3734 surviving men (80% participation rate) took part in the first dementia screening in 1991–1994, and of these, 2704 individuals participated in the 1994–1996 follow-up.

The autopsy sub-study was established in 1991 as part of the HAAS study [26]. All consenting participants were eligible but there was a special effort to recruit subjects diagnosed with dementia. The study was approved by the Institutional Review Board of the Kuakini Medical Center, the Honolulu Department of Veterans Affairs and the National Institute for Occupational Safety and Health. Written informed consent was signed by the study participants or by a family representative when subjects were demented.

2.2. Dementia assessment

In 1991 and 1994 participants were screened for dementia using a three-step procedure. The Cognitive Abilities Screening Instrument (CASI) [32] was administrated to the whole cohort. The CASI score, which ranges from 0 to 100, is a well-recognized instrument for the assessment of cognitive function validated among Japanese and Western sample populations [8]. CASI score, age and education were used to select a subgroup of participants for further dementia evaluation [12,35]. Clinical evaluation of dementia included a proxy interview, detailed neuropsychologic assessment, a neurologic examination, neuroimaging and blood tests. A final consensus diagnosis for dementia was given by the study neurologist and at least two other physicians expert in geriatric medicine. Dementia was diagnosed according to DSM-III R criteria [1], probable and possible AD by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [21]; VaD by the California Alzheimer's Disease Diagnostic and Treatment Centers guidelines [3].

2.3. Autopsy sub-study

At the time of this analysis, autopsy dataset specimens were available on 471 men. Autopsied subjects were similar to non-autopsied decedents with regard to many characteristics, including cancer, cardiovascular diseases and age. Details on the autopsy and neuropathological protocols are reported elsewhere [26,27]. Briefly, evaluation of the brain infarcts was performed in the parenchymal and meningeal tissue from the neocortical areas. Brain infarcts are described as circumscribed ischemic areas with reduced number of neurons, pale appearance and noticeable gliosis. These lesions were classified by the extent of the tissue damage as *large infarcts* (lesions larger than 1 cm) or lacune (*small infarcts*) (lesions 1 cm or smaller). *Large* and *small infarcts* were identified during the macroscopic examination. Microscopic examinations were done on 32 brain regions [26]. *Microinfarcts* lesions visible only in the microscopic exam, typically 50–400 μm in diameter [34], were counted throughout the brain. Diffuse (DP) and neuritic plaques (NP) were counted in five fields from the hippocampus CA1 and subuculum areas and five fields from the four areas of the neocortex (middle frontal gyrus, inferior parietal lobule, middle temporal gyrus, and occipital cortex). NP were defined as plaques containing dystrophic sliver-positive neuritis and those without neurites were classified as DP. Fields were selected for counting from areas with the highest numbers of lesions; those with highest counts (DP or NP/mm^2) were taken to represent the cortical or hippocampal area. The evaluation was performed by one of the neuropathologists blinded to clinical information. Cerebral amyloid angiopathy (CAA) in the parenchyma of the neocortical tissue was evaluated by βA4 amyloid immunostaining and graded from "mild" to "severe" depending on the number of positive vessels per area [33].

2.4. Measure of covariates

Several covariates assessed during mid- and late-life were considered. Age at the fourth exam in 1991 and education were included in the analysis. For several biological measurements we used mid-life values because they are less influenced by preclinical dementia status. Mid-life blood pressure (BP) was the mean BP of the first three exams, and late-life

BP was the value measured at the 4th exam in 1991. Mid-life smoking status was categorized as never, former and current, and pack/years of cigarette exposure, alcohol intake as drinks/day (none, <1 [13.2 g], 1–2 and ≥3). Stroke and coronary heart disease (CHD) history were reported at baseline in 1965 and monitored throughout the entire follow-up by active surveillance as describe elsewhere [15]. Type 2 diabetes, defined according to the World Health Organization criteria [37] included individuals with previously diagnosed type 2 diabetes, those taking oral hypoglycemic agents or insulin, and those with a fasting blood glucose ≥7.0 mmol/l (126 mg/dl) or with a 2-h post-load glucose ≥11.1 mmol/l (200 mg/dl) as measured in 1991. Ankle brachial index (ABI) measured in 1991 was used as cumulative measure of peripheral vascular disease. ABI values were dichotomized with a cutoff of 0.9; values below this point were interpreted as an indicator of generalized atherosclerosis [24]. Apolipoprotein E genotype was performed as previously described [13]. Participants were categorized as ApoE ε4-positive if they carried at least one copy of the ε4 allele and ε4-negative otherwise.

2.5. Case and control selection

Sample selection was previously described [41]. Briefly, 361 cases of dementia were diagnosed at the baseline screening (226 prevalent cases) and at the follow-up (135 incident cases). Among them, 295 cases (181 prevalent cases and 114 incident cases) had specimens available for DNA extraction. The study cases included 179 subjects diagnosed with AD and 104 cases of VaD. There were 12 cases with other types of dementia; this group was excluded from the analysis.

Compared to the dementia cases with no DNA, the study cases included a higher percentage of AD cases with cerebrovascular disease (CVD) and VaD cases, and a lower percentage of AD subjects without CVD. The cases included in this study did not differ from the rest of the cases in the cohort in demographic and health related characteristics, except there was a higher prevalence of type 2 diabetes.

To obtain a control group frequency-matched by age with the case group, one control per case was randomly selected within the same 5-year age-category. To increase the power to analyze the association between neuropathological outcomes and genetic information, additional non-demented subjects with neuropathological data were included, giving a total of 648 controls. As a result of the frequency matching, the selected controls were on average 3 years older than the rest of the non-demented cohort; however demographic and health related characteristics were similar.

To reduce the possibility that the control group included subjects with possible incipient cases of dementia, we created a separate category of "low cognitive score" (LCS). Non-demented subjects in this group ($n = 131$, 20.2% of the total sample) had a CASI score decline greater than 4.00 points between the baseline and the follow-up (equivalent to the group mean decline in CASI + 1 standard deviation).

2.6. DNA genotype

Genomic DNA was extracted from cryo-preserved peripheral white blood cell pellets according to standard protocols. Genotype analysis was first performed in a subgroup of 30 subjects to evaluate the allele frequencies of four different SNPs in the TGF-β1 gene. We excluded from further analyses the SNPs −800G → A and +74G → C (encoding for an arginine → proline substitution at codon 25) because the frequency of the mutant allele was <5%. The +29T → C and the −509C → T SNPs were more frequent in the sample, so the genotype analysis was completed in the whole sample. Genotyping was performed utilizing polymerase-chain reaction-based amplification and restriction fragment length polymorphism (PCR-RFLP) method for the −800G → A, the +74C → T and the +29T → C [19,20]. The PCR-Taqman® procedure was used for the −509C → T SNP [14]. Fifty-four DNA samples (5.8%) could not be genotyped and were excluded from the analysis. Compared to the rest of the samples, those with no genotype had a significantly lower initial DNA concentration and included more demented cases, although the difference was not significant.

2.7. Statistical analysis

The study sample with complete genotype information included 261 cases of dementia (including 162 AD cases and 99 VaD cases), 125 LCS subjects and 491 non-demented individuals. Autopsy information was available in a subsample of 282 subjects. The study sample allowed the detection of at least a two-fold decrease or increase in the risk of dementia, AD or VaD assuming a genotype frequency ≥0.30 and an additive effect of the mutant allele on the disease, with a type I error (α level) of 5% and a power (1-β) of 80%.

Allele frequencies were estimated and the χ^2-test was used to identify significant departure from the Hardy–Weinberg equilibrium separately in cases and controls. Linkage disequilibrium test between the two SNPs showed evidence for a partial linkage disequilibrium [5] ($D' = 0.86$, $r^2 = 0.72$) but there were no independent association between the −509C → T and dementia or any type of neuropathologies. Characteristics of the study by case status were previously published [41]. Baseline characteristics were compared by the +29 SNP genotypes using an age-adjusted general linear model for continuous variables and an age-adjusted logistic regression for dichotomous outcomes. A multinomial logistic regression was used to assess the association between TGF-β1 and the risk of dementia, so the odds ratio (OR) and the 95% confidence interval (CI) for LCS, AD and VaD were calculated simultaneously. The effect of the +29T → C polymorphism was tested according to an additive genetic model (TT = 0, TC = 1, CC = 2) and two distinct OR estimates (OR_{TC} and OR_{CC}) were calculated. Analyses were adjusted for potential confounders.

Two different models were examined: the first model included age and age squared at the fourth exam, education, and ApoE ε4 status. The −509C → T SNP was included as a covariate in the analysis so any observed association between the +29T → C and dementia was not confounded by this second SNP. In the second model cardiovascular risk factors and diseases were added. Diastolic blood pressure, alcohol intake and smoking status were tested but excluded from the final analysis because they made no significant contribution to the model. To assess the robustness of the results we performed 10,000 permutation tests using a Monte-Carlo permutation framework to generate an empirical p value. The test compares the initially observed p value of the study to the distribution of the p values from 10,000 simulated tests. These simulate p values are obtained by permuting, at random, the genotype–phenotype data so that the final p-value is estimated by the proportion of permutations for which the permutated data test statistic is greater than the initially observed test statistic.

To maximize statistical power *large*, *small* and *microinfarcts* and CAA were dichotomized (absent/present). NP were dichotomized (<4 and ≥4 mm^{-2}) based on the CERAD criteria for neuropathological diagnosis of probable AD [23]; for comparison, DP were categorized in the same way. A logistic regression model was used to estimate the OR for the different neuropathological outcomes. The analysis was adjusted for age at death, education, mid- and late-life systolic blood pressure, ApoE ε4 status, dementia status, ABI, history of CHD, stroke; additionally the models for the DP and NP were adjusted for the presence of CAA. Statistical analysis was performed using STATA Software Version 7.0 (Stata, College Station, TX).

3. Results

3.1. Clinical outcomes

In the total sample the frequencies of the +29 TT, TC and CC genotypes were 23.3, 48.8 and 27.9%, respectively and in both cases and controls genotype frequencies were in agreement with Hardy–Weinberg equilibrium. Baseline characteristics were similar among genotypes except that the CC genotype group had higher percentage of coronary heart disease compared to the other two groups (Table 1).

Table 1
Characteristics of the sample by TGF β1 + 29T → C genotype: the HAAS

	TT (N = 206)	TC (N = 425)	CC (N = 246)
Age at exam 4	81.0 (0.4)	80.0 (0.2)*	80.5 (0.3)
Education (years)	9.8 (0.2)	9.8 (0.2)	10.1 (0.2)
Mid-life			
SBP (mmHg)	134.8 (1.2)	134.2 (0.8)	133.1 (1.1)
DBP (mmHg)	83.0 (0.7)	82.7 (0.5)	82.0 (0.6)
Alcohol (g/day)[a]	11.4 (1.5)	12.0 (1.0)	12.3 (1.4)
Current smokers (%)	29.8	29.8	26.8
Late-life			
SBP (mmHg)	151.7 (1.8)	150.7 (1.2)	151.1 (1.6)
DBP (mmHg)	79.5 (0.8)	79.6 (0.6)	78.4 (0.8)
ApoE ε4 (%)	16.1	20.2	18.2
Prevalent disease			
Type 2 diabetes (%)	36.4	36.9	34.5
ABI < 0.9 (%)	22.5	27.6	23.3
CHD (%)	21.1	21.9	29.6*
Stroke (%)	13.7	12.3	15.3
Dementia (%)	31.6	28.9	27.9

Data are mean value (standard error) unless otherwise specified.
[a] Non-drinkers were excluded (n = 274). SBP: systolic blood pressure; DBP: diastolic blood pressure; ABI: ankle brachial index; CHD: coronary heart disease. *Mid-life* measurements are from the first three exams (1965–1966, 1967–1970, 1971–1974; mean age = 55 years); *Late-life* measurements are from the fourth exam (1991–1994; mean age = 78 years).
* $p < 0.05$ for the age-adjusted comparison with the TT group.

Allele frequencies were similar among cases and controls, but the frequency of the combined TC + CC genotypes was lower in VaD cases (69.7%) compared to the controls (78.6%) (p = 0.05) (Table 2). Compared to the reference TT genotype there was a significantly decreased risk for VaD for those with the CT and the CC genotypes (OR_{CT} = 0.28, CI: 0.1–0.9; OR_{CC} = 0.28, CI: 0.1–0.9) (Table 3); the results from the 10,000 permutation tests produced significant results (p = 0.0067 and 0.0029, respectively). The risk for AD and LCS was reduced in those with CT and CC genotypes but this was not significant.

3.2. Autopsy outcomes

The CC genotype was significantly associated with a reduced risk of *microinfarcts* (OR_{CC} = 0.31, p = 0.007)

Table 2
Allele and genotype frequency (N (%)) of TGF-β1 + 29T → C: the HAAS

Allele	Non-demented (N = 982), N (%)	AD (N = 324), N (%)	p	VaD (N = 198), N (%)	p	LCS (N = 250), N (%)	p
T	454 (46.2)	156 (48.1)		103 (52.0)		124 (49.6)	
C	528 (53.8)	168 (51.9)	0.55	95 (48.0)	0.14	126 (50.4)	0.34
Genotype	**Non-demented (N = 491), N (%)**	**AD (N = 109), N (%)**	**p**	**VaD (N = 99), N (%)**	**p**	**LCS (N = 125), N (%)**	**p**
TT	105 (21.4)	38 (23.5)		30 (30.3)		33 (26.4)	
TC	244 (49.7)	80 (49.4)		43 (43.4)		58 (46.4)	
CC	142 (28.9)	44 (27.2)	0.83	26 (26.3)	0.15	34 (27.2)	0.49
TC + CC	386 (78.6)	124 (76.5)	0.58	69 (69.7)	0.05	92 (73.6)	0.23

χ^2 and p-values are and from the comparison with the non-demented group.

Table 3
Logistic regression analysis for the risk of Alzheimer's disease, vascular dementia and "low cognitive score" associated with TGF-β1 + 29 genotypes T → C: the HAAS

	AD, OR (95% CI)	VaD, OR (95% CI)	LCS, OR (95% CI)
Model 1[a]			
TC	0.51 (0.2–1.3)	0.34 (0.1–1.0)	0.84 (0.3–2.2)
CC	0.52 (0.2–1.4)	0.33 (0.1–0.9)	0.57 (0.2–1.6)
Model 2[b]			
TC	0.46 (0.2–1.2)	0.28 (0.1–0.9)	0.91 (0.3–2.4)
CC	0.49 (0.2–1.3)	0.28 (0.1–0.9)	0.60 (0.2–1.7)

Results are odds ratios (95% confidence interval) for the risk of dementia and low cognitive score for the TC and the CC genotype compared to the TT genotype.

[a] Model 1 was adjusted for age and age squared at the fourth exam, education, Apo ε4 status, TGF-β1-509 genotype.

[b] Model 2 was adjusted as model 1 plus mid-life and late-life systolic blood pressure, ankle brachial index, coronary heart disease, stroke, type 2 diabetes.

(Table 4). The risk of *small infarcts* was similar to the risk for *microinfarcts* but not significant. The +29 CC genotype was also associated with a reduced risk for CAA and with an increased risk for DP and NP of the neocortex; the association with DP and NP in the hippocampus was similar but not significant.

4. Discussion

The present study examined the effect of the +29T → C polymorphism of the TGF-β1 on dementia and related neuropathologies. The +29T → C mutation causes an amino acid change (leucine → proline) that could influence the intracellular trafficking and the export of the protein latent form [4,30], furthermore and the C allele has been associated with higher levels of circulating TGF-β1 [30,39].

Our results suggest that the C allele at the +29 locus is associated with a reduced risk for vascular dementia and related lesions. The autopsy results showed that the same allele was associated with a reduction of *microinfarcts* and possibly with *small infarcts,* but not with *large infarcts*, indicating a possible effect of this allele on the small vessel type of lesions rather than larger ones. Correlation analyses demonstrated a strong association of *microinfarct*s with *small infarcts* and a weaker association with *large infarcts*; in addition previous analysis on this autopsy sample indicated a robust relationship between *microinfarcts* and diagnosis of dementia [34]. Indeed, the observed protective effect of the C allele was mainly in VaD cases without large vessel stroke (data not shown), suggesting that the cases of dementia associated with this polymorphism may be the result of ischemic events in the small vessels.

These data also suggest a link between +29C allele and a reduced risk for clinical AD but not for the classic neuropathological markers of AD. Cerebrovascular pathologies, in particular *microcerebral infarcts*, are often present in AD cases [16]. Possibly the C allele protects the small vessels in the brain and reduces cerebrovascular diseases that contribute to AD. Interestingly, the CC genotype was associated with a reduced risk of CAA, this result is in agreement with another study on a different Japanese sample [11], no other observational study has been reported. TGF-β1 has been linked to an increased vascular extracellular matrix deposition but also to a protective effect on the endothelium [17]; the observed effect of TGF-β1 on CAA could be mediated by the protective action on the endothelium. *In vivo* and *in vitro* data on the role of TGF-β1 in the CAA pathology are still contradictory [38].

In the brain, TGF-β1 has a primary protective role after a cerebral ischemic event [6]. Animal studies showed an elevation of TGF-β1 mRNA transcript in the cortex and

Table 4
Logistic regression analysis for the risk of different pathological outcomes associated with TGF-β1 + 29T → C genotypes: the HAAS

Genotype	TT		TC		CC	
Outcome	*N*[a] (%)	OR	*N*[a] (%)	OR (95% CI)	*N*[a] (%)	OR (95% CI)
Infarct						
Micro	19 (32.8)	1	46 (30.4)	0.87 (0.4–1.7)	13 (16.7)	0.31 (0.1–0.7)
Small	33 (56.9)	1	68 (45.0)	0.58 (0.3–1.1)	39 (45.3)	0.62 (0.3–1.2)
Large	16 (27.6)	1	40 (26.5)	0.86 (0.4–1.9)	36 (41.8)	2.17 (0.9–4.9)
CAA	32 (55.2)	1	66 (43.7)	0.55 (0.3–1.1)	32 (37.2)	0.48 (0.2–0.9)
DP[b]						
Hippocampus	11 (19.6)	1	32 (23.0)	0.85 (0.3–2.3)	22 (28.6)	2.51 (0.9–7.2)
Cortex	26 (46.4)	1	67 (47.2)	1.33 (0.6–3.1)	42 (54.5)	2.83 (1.1–7.3)
NP[b]						
Hippocampus	8 (14.3)	1	25 (18.0)	1.18 (0.4–3.4)	15 (19.5)	2.04 (0.7–6.2)
Cortex	14 (25.0)	1	34 (23.9)	1.20 (0.5–3.0)	28 (36.4)	4.34 (1.6–11.8)

Results are odds ratios (95% confidence interval) associated with the TC and the CC genotype compared to the TT genotype. Analysis adjusted for age at death, education, mid-life and late-life systolic blood pressure, Apo ε4 status, dementia status, ankle brachial index, coronary heart disease, stroke and type 2 diabetes.

[a] Number of cases and their frequency among the genotype carriers.

[b] The model included the previous covariates plus CAA. NP: neuritic plaques; DP: diffuse plaques.

hippocampus following ischemia [18], and administration of exogenous TGF-β1 reduced brain infarct size caused by a thromboembolic stroke [9,10]. The reduction in infarcted areas is characterized by reduced activation of the microglia [22]. Furthermore, the administration of TGF-β1 during an ischemic event preserved mice learning ability suggesting a potential role of this molecule in the protection of the ischemic-related neurological degeneration [36].

The study participants are all first generation immigrants from Japan and shared a similar genetic, environmental and cultural background, reducing confounding by population stratification that sometimes clouds the interpretation of genetic association studies. We also controlled for several potential confounders associated with inflammatory-related mechanisms such as blood pressure, coronary heart disease, stroke and type 2 diabetes. Our sample provided a unique opportunity to investigate the association of this polymorphism with several outcomes, including clinical dementia and possible pathologic substrates for the disease, which are rarely investigated by genetic studies on dementia.

Additional aspects of the study should be considered. In the present study the association between a polymorphism of the TGF-β1 and the two major subtypes of dementia, low cognitive function, and related neuropathologies has been tested in the same population. This approach offers a unique opportunity to test risk factors for closely related phenotypes, but it could also cause false positive results due to multiple testing. We did not apply a Bonferroni correction for multiple testing, as it would be too conservative a test, i.e. it fails to consider the correlation among phenotypes [25]. The Permutation test, which we did use, provides an empirical method to correct the *p*-values from multiple testing [25]. However, replication of the results in a different cohort with sufficient cases of vascular dementia provides the best evidence for association; at the present our results can generate a testable hypothesis on the role of TGF-β1 in small vessel disease. The dataset included men only; however we do not hypothesize any interaction of TGF-β1 + 29 with gender. As with other Japanese samples, the frequency of VaD and AD with microcerebrovascular complications is higher than in Caucasians: in our sample there is a weaker association between AD and neuritic plaques and higher between AD and microinfarcts [26]. Genetic and environmental factors may be different in the Japanese-American men compared to other populations so caution is needed in the extension of these results to other ethnic groups. The sample size for dementia sub-types was moderate, causing a potential type-I error. While this is possible, the results show a consistency between the clinical expression of dementia and the various neuropathological outcomes.

In conclusion, this pilot study examines TGF-β1 genetic variants and different dementia types and neuropathological outcomes at the same time, the results are consistent with a possible role of a genetic polymorphism of TGF-β1 in dementia, particularly of the vascular-related type suggesting a difference in the inflammatory mechanisms associated with AD pathology and small vessel pathway. Replication of these findings is needed in different population-based samples with vascular dementia cases and neuropathological data.

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