Received: 6 September 2023 | Accepted: 29 November 2023

DOI: 10.1002/agm2.12278

Aging Medicine Open Access WILEY

ORIGINAL ARTICLE

Involvement of single nucleotide polymorphisms of junction adhesion molecule with small vessel vascular dementia

Peter Xie[1] | Kiran Kancherla[1] | Sashiruben Chandramohan[1] | Nady Braidy[1,2,3] | Eunice Kar Wing Chan[4] | Ying Hua Xu[1,2,5] | Daniel K. Y. Chan[1,2,5]

[1]Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

[2]Ingham Institute, Liverpool, New South Wales, Australia

[3]Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia

[4]Faculty of Medicine, Western Sydney University, Macarthur, New South Wales, Australia

[5]Department of Aged Care and Rehabilitation, Bankstown Hospital, Bankstown, New South Wales, Australia

Correspondence
Daniel K. Y. Chan, University of NSW, Department of Aged Care and Rehabilitation, Bankstown Hospital, Bankstown, New South Wales 2200, Australia.
Email: d.chan@unsw.edu.au

Abstract

Objectives: It is now recognized that blood brain barrier (BBB) leakage occurs in cerebral small vascular disease (CSVD) and plays a significant role in the pathophysiology of vascular dementia. We hypothesized that genetic polymorphisms of junctional adhesion molecule-A (JAM-A) (which may result in compromised structure of tight junction proteins that form the BBB) in combination with cerebrovascular risk factors hypertension, lipid disorders, and type 2 diabetes may result in BBB leakage and increase the individual's risk of CSVD-related dementia.

Methods: In this case–control study, 97 controls with a mean Mini-Mental State Exam (MMSE) score of 29 and 38 CSVD-related vascular dementia participants (mean MMSE score of 19) were recruited. Bloods were collected for the analysis of two common single nucleotide polymorphisms (SNPs) of the JAM-A genotypes rs790056 and rs2481084 using real-time polymerase chain reaction (PCR) assay. Medical history of hypertension, hyperlipidemia, and diabetes was collected for all participants.

Results: Polymorphisms of genotype JAM-A SNP rs790056 showed statistically significant result when the subgroup with hyperlipidemia was analyzed (OR = 3.130, $p = 0.042$ for TC + CC genotypes with hyperlipidaemia vs controls). Similar result was found with diabetes (OR = 4.670, $p = 0.031$ for TC + CC genotypes vs controls). No significant result was found with hypertension. Borderline results of statistical significance were found for JAM-A SNP rs2481084 with hyperlipidemia (OR = 3.210, $p = 0.054$ for TC + CC genotypes vs controls) and with diabetes (OR = 3.620, $p = 0.069$ for TC + CC genotypes vs controls) but not for hypertension. The borderline results might have been due to lack of statistical power because of small sample size.

Conclusions: These results lend further support that cerebrovascular risk factors interact with genetic polymorphisms of BBB proteins to increase the risk of vascular dementia.

KEYWORDS
blood brain barrier, dementia, vascular

1 | INTRODUCTION

Vascular dementia (VaD) is the second most common type of dementia, accounting for approximately 15% of all dementia.[1] It is a neurological condition that affects executive and cognitive functions like judgment, reasoning, memory, and language. In addition, mood and behavioral changes can occur as may gait disturbance.[2]

It is now recognized that one form of VaD is caused by widespread injuries to cerebral small vessel disease (CSVD) associated with vascular risk factors such as hypertension, high cholesterol, and diabetes.[3,4] Chronic small vessel damage in the brain may result in diffuse white matter hyperintensities visible on MRI. This is corroborated in postmortem patients with findings of lacunar infarct demonstrating arterial wall thickening (lipohyalinosis and fibrinoid necrosis) and fluid leakage around the arterial wall.[5] The pathological mechanism proposed is a diffuse process involving damage to endothelium and loss of blood brain barrier (BBB) integrity. The increased permeability of the BBB allows fluid from plasma to leak into interstitial brain tissue. The extravasation allows cytokines and chemokines to penetrate BBB, causing neuroinflammation to neurocircuits in the white matter of the brain.[3,5,6]

In addition, further evidence of blood brain barrier leakage in patients with VaD[7] is supported by the finding that older patients who developed VaD had higher CSF/serum albumin ratio before developing dementia compared with those who remained cognitively intact.[8]

If indeed the breakdown of blood brain barrier is associated with CSVD, then abnormal tight junction protein of the blood brain barrier (that have formed from genetic polymorphism) may be associated with higher risk of CSVD-related VaD.

Tight junctions (TJ) in the blood brain barrier are known to limit penetration of circulating blood from reaching the brain substance and thus preventing neuroinflammation from occurring. Junctional adhesion molecules (JAM) are a member of CD2 subgroup of immunoglobulin superfamily recognized by two immunoglobulin-like folds, V and C2 domains in the extracellular region, and are attached to a single transmembrane domain and a short cytoplasmic tail. Three forms of junctional adhesion molecules—JAM-A, JAM-B, and JAM-C—are encoded by genes found on different chromosomes. Junctional adhesion molecules are mainly found between junctions of endothelial and epithelial cells, as well as the surface of leucocytes, monocytes, lymphocytes, erythrocytes, and platelets. Through their domain-binding motif, junctional adhesion molecules can interact with other TJ molecules such as claudin.[9]

JAM-A is highly expressed in the brain endothelial cells and plays a role in regulating leucocyte trans-endothelial migration and paracellular permeability.[10] Formation of homophilic-trans interactions on the extracellular domain allows JAM-A to increase occlusion of paracellular spaces. A study in a rat cortical cold injury model of the brain showed lack of endothelial JAM-A immunoreactivity, providing evidence that JAM-A contributes to tight junction integrity. Therefore, its altered expression could cause BBB breakdown following brain injury.[11] In more detail, under normal conditions, JAM-A maintains BBB integrity, but in inflammatory conditions it regulates interactions between leucocytes and endothelial cells, acting as a leukocyte adhesion molecule. Inflammation causes redistribution of JAM-A away from endothelial junctions to the apical cell surface where they bind to lymphocyte function-associated antigen-1 (LFA-1) on leucocytes via chemokine-triggered conditions. This interaction allows leucocyte adhesion to endothelium and subsequent trans-endothelial migration into inflamed regions such as brain tissue.[12]

2 | METHODS

2.1 | Study design and ethics

This is a case–control study. Ethics were obtained from South Western Sydney Local Health District Human Research Ethics Committee (HREC/16/LPOOL/199). All participants consented and all responses to questionnaires and blood samples were collected in accordance with the ethical guidelines.

2.2 | Setting

Control participants were recruited from outpatient clinics and geriatric wards at Bankstown-Lidcombe Hospital and the community, while vascular dementia patients were recruited from memory disorder clinic or geriatric wards at Bankstown-Lidcombe Hospital.

2.3 | Inclusion and exclusion criteria

2.3.1 | Inclusion criteria

All participants were required to be above the age of 65 years. Control participants were screened for cognitive impairment and with an inclusion criterion of Mini-Mental State Exam (MMSE) score of over 27 and CSVD-related VaD patients were included after stringent diagnostic consideration (see 2.3.3).

2.3.2 | Exclusion criteria

Patients who were younger than 65 years old or with the diagnosis of predominantly other types of dementia (such as Alzheimer's disease) were excluded. Controls were excluded if found to have any cognitive impairment, dementia diagnosis, or evidence of cerebrovascular pathology either through history or imaging.

2.3.3 | Diagnostic consideration

The diagnosis of CSVD-related VaD was stringent and made on clinical grounds with the support of at least one imaging

modality—MRI, CT, or SPECT—to corroborate with the clinical diagnosis of VaD being the predominant dementia. The diagnosis was made by at least one experienced geriatrician or psychogeriatrician. VaD participants with an AD component were only included if their dementia was predominantly of vascular etiology, both on clinical grounds and evidence of neuroimaging. An independent geriatrician's opinion was sought for uncertain cases and such participants were only included if both geriatricians were in consensus of the CSVD diagnosis.

Key considerations in the clinical diagnosis were a history of the participant's signs and symptoms obtained from both participant and carer, and a medical history of vascular risk factors like type 2 diabetes mellitus (T2DM), hypertension, and lipid disorders. The medical history was confirmed with patients' general practitioner or hospital medical records. Special attention was paid to existing conditions like hypertension, diabetes, and lipid disorders. Serial MMSE scores were also used, with a worsening of the score over time more likely to favor a VaD diagnosis. Cerebral small vessel VaD diagnosis was made if there was evidence of lacunes and/or extensive periventricular white matter lesions. Further details can be found in our previous publication.[13]

2.4 | Survey of lifestyle factors

Participants and carers responded to a questionnaire on lifestyle factors and medical history. The questionnaire included questions on demographics and socioeconomic status, current medications, family history, diet, physical activity, hobbies, smoking, drinking, and activities of daily living, as well as medical history that was counterchecked with participants' carers and medical records (hospital or general practitioners) for accuracy. A translator was also used for patients with difficulties communicating in English.

2.5 | Blood collections

A total of 10 mL of venous blood was collected from participants by venipuncture and separated into two vacutainer blood tubes: plain tube for biochemical assay and EDTA tube for DNA extraction. For biochemical assay, serum was separated within 1 h of blood collection by centrifugation. DNA was isolated from EDTA blood using Qiagen DNeasy Blood & Tissue Kit (Qiagen). Both serum and DNA were stored at −80°C until analysis. Coded samples were processed by laboratory personnel blinded to participants' clinical characteristics.

2.6 | Genetic analysis of SNPs

Junction adhesion molecule SNPs were selected from the HapMap database (International HapMap Project, 2015).[14] Haploview 4.0 software[15] was used to select SNPs with $r^2 \geq 0.8$ and a minor allele frequency ≥0.05. This led to the identification of 2 SNPs with a mean r^2 of 0.975. The SNPs *rs790056* and *rs2481084* in the junction adhesion molecule-A genotyping were performed in LightCycler2.0 real time PCR (Roche, Germany) using LightSNiP reagent (coupled with primer and probe, TIBMOLBIO, Germany) and FastStartDNA Master HybProbe (Roche Diagnostics GmBH, Mannheim, Germany). Genotyping was performed using custom-made LightSNiP assays for *rs790056* and *rs2481084* that were purchased from TIB Molbiol (Berlin, Germany). Each LightCycler capillary tube contained 9 µL of a PCR master mix that contained LightSNiP reagent and other reagents essential to PCR. One microliter of DNA was added to each sample and centrifuged at 2000 g for a few seconds to force the mixture to the bottom of the capillary tube. PCR was performed with an initial denaturing step at 95°C for 15 s, followed by 50 cycles of denaturation at 95°C for 2 s, annealing at 68°C for 3 s, and extension at 72°C for 10 s. Transition rates between temperatures were set at 20°C per second. After PCR amplification of the genomic region of interest, LightSNiP assays (TIB Molbiol) employed fluorescently labeled probes to generate a genotype-specific melting curve pattern when running a temperature ramp. Fluorescence was acquired one time every cycle at the end of the extension step. The high-resolution melting curve data obtained from the HR-I instrument were normalized and temperature corrected using a program written in Lab VIEW (National Instruments Corporation, Austin, TX). The resulting melting peak (−dP/dT vs temperature) plots were used to assign the JAM-A genotype to the DNA samples. Genotyping was significant if the success rate for the SNP was ≥85% and the genotype distribution fit within the Hardy–Weinberg equilibrium (HWE) ($p > 0.050$ for χ^2 test between expected and observed values) in the control groups. The online Finetti HWE calculator was used to test for Hardy–Weinberg equilibrium.[16]

2.7 | Statistical analysis

All collected data, including questionnaire and genetic analysis results, were recorded into a Microsoft Access 2007 database. The data were analyzed using SPSS (IBM SPSS Statistics 22) and GraphPad Prism 6. Dichotomous variables were shown as numbers with percentages in the parentheses. A Fisher's exact test was used to compare the differences in environmental risk factors and genotypes of the single-nucleotide polymorphisms of JAM-A between the two population groups. A nonparametric Mann–Whitney *U* test was used to interpret ranking data, e.g., MMSE scores. A *p* value of <0.050 was considered statistically significant.

3 | RESULTS

3.1 | Demographic data

There were 97 controls with a mean age of 84.3 ± 4.89 years and 38 CSVD VaD patients with a mean age of 81.3 ± 6.14. The mean MMSE scores for controls and CSVD patients were 29.1 ± 1.08 and 19.1 ± 5.36, respectively. While there was no significant difference

in gender between the population groups, there was a significant difference in age, with the controls being older. There was also a significant difference in MMSE scores with $p<0.001$. Further details across the two groups are outlined in Table 1.

3.2 | Hypertension, hyperlipidemia, and diabetes

A comparison of cerebrovascular risk factors, including hypertension, hyperlipidemia, and type 2 diabetes mellitus (T2DM), between control and CSVD VaD groups is summarized in Table 1. There was no significant difference in the proportion of patients with a history of hypertension between control and VaD participants. However, a significantly higher proportion of VaD participants had history of lipid disorder and/or diabetes.

3.3 | Genotypic polymorphism analysis alone

Table 2 summarizes the genotype frequencies for SNPs of JAM-A (rs790056 and rs2481084). An analysis of categorical genotype data was carried out using logistical regression models to further investigate genotype associations. The odds ratio and *p* value are presented for each individual genotype of the 2 SNPs in Table 2. Genotypes of JAM-A SNPs rs790056 and rs2481084 did not show statistically significant different distribution patterns between CSVD patients and controls when genetic polymorphism was analyzed alone.

3.4 | Stratified analysis of genotypic polymorphism with hypertension, hyperlipidemia, and diabetes

Stratified analysis was then performed to find any clinical significance by combinatorial effects between genotypes and cerebrovascular risk factors—hypertension (HBP), hyperlipidemia, and type 2 diabetes (Tables 3–5).

For lipid disorders, we observed an association between combined haplotypes TC+CC of rs790056 and CSVD (OR=3.130, $p=0.042$, 95% CI=1.080–9.100) when compared to controls. For type 2 diabetes, we found certain combined genotypes of SNPs in JAM-A was associated with VaD. The odds ratio of VaD increased significantly in TC+CC of rs790056 (OR=4.670, $p=0.031$, 95% CI=1.280–17.000 respectively). Having a variant genotype of JAM-A rs790056 appeared to increase the risk of development of CSVD in individuals with either diabetes or hyperlipidemia disorder.

Results that just missed statistical significance were found when analyzing TC+CC genotypes of rs2481084 with hyperlipidemia (OR=3.210, $p=0.054$) and with diabetes (OR=3.620, $p=0.069$) and VaD when compared to controls. No significant association was found with hypertension in either rs790056 or rs2481084.

4 | DISCUSSION

JAM-A is a key component of tight junctions of BBB and its genetic polymorphism may play a role in hypertension. In a Hong Kong study of 650 patients, Ong et al. found an association between the levels of plasma JAM-A and hypertension.[17] It also found JAM-A may be associated with upstream transcription factor 1 (USF1), a gene involved in glucose and lipid metabolism pathways. Certain SNPs of the gene upstream transcription factor 1 (USF1) are located on the promotor region of JAM-A. In our current study, no interaction between hypertension and JAM-A polymorphisms in association with CSVD-related VaD was found.

Although we found no association of CSVD-related VaD with JAM-A when genetic polymorphism was studied in isolation, the association became apparent when stratification of cerebrovascular risk factors such as diabetes and lipid disorder were taken into account. This combinatory effect of genetic polymorphism and cerebrovascular risk factors in the increase of CSVD-related VaD risk is further echoed in our previous study.[13] Stratification analysis in the aforementioned study[13] revealed that having combined genotypes GC+CC of claudin-1 rs893051 and lipid disorders was associated with higher risk of CSVD-related VaD (OR=9.900, $p<0.001$) when compared to controls. Likewise, when compared to controls, the odds ratio of CSVD VaD increased significantly in persons who have diabetes and the GC+CC genotypes of claudin-1 rs893051 (OR=12.570) or diabetes and the GT+TT of rs17501010 (OR=5.330).

TABLE 1 Demographic characteristics of controls and CSVD patients.

	Control ($n=97$)	CSVD ($n=38$)	*p*	OR, 95%CI
Age	84.3±4.89	81.3±6.14	0.011*	0.930–4.992
Gender				
Female	56 (57.7)	21 (55.3)	0.848	OR 1.106, 0.519–2.354
Male	41 (42.3)	17 (44.7)		
MMSE	29.1±1.08	19.1±5.36	0.000***	
Lipid disorder	44 (45.4)	25 (65.8)	0.037*	OR 2.316, 1.061–5.055
Diabetes	17 (17.5)	13 (34.2)	0.042*	OR 2.447, 1.046–5.272
Hypertension	58 (59.8)	28 (73.7)	0.165	OR 1.883, 0.822–4.310

Note: *$p<0.05$; ***$p<0.001$.

TABLE 2 Genetic frequency of selected JAM-A SNPs.

Genotypes		Control ($n=97$)	CSVD ($n=38$)	OR	95%CI	p
rs790056	TT	51 (52.6)	16 (42.1)	Reference		
	TC	40 (41.2)	18 (47.4)	1.434	0.651–3.162	0.371
	CC	6 (6.2)	4 (10.5)	2.125	0.532–8.482	0.286
rs2481084	TT	58 (59.8)	20 (52.6)	Reference		
	TC	30 (30.9)	14 (36.8)	1.353	0.600–3.051	0.466
	CC	9 (9.3)	4 (10.5)	1.289	0.357–4.649	0.698

TABLE 3 Stratified analysis: hypertension (HBP).

HBP		Control	CSVD	OR	95%CI	p
	rs790056					
No	TT	19	6	Reference		
	TC+CC	20	4	0.633	0.154–2.601	0.725
Yes	TT	32	10	0.990	0.310–3.159	1.000
	TC+CC	26	18	2.192	0.732–6.569	0.194
	rs2481084					
No	TT	21	6	Reference		
	TC+CC	18	4	0.778	0.189–3.197	1.000
Yes	TT	37	14	1.324	0.442–3.964	0.786
	TC+CC	21	14	2.333	0.752–7.237	0.176

TABLE 4 Stratified analysis: lipid disorders.

Lipid disorder		Control	CSVD	*OR*	95%*CI*	*p*
	rs790056					
No	TT	26	7	Reference		
	TC+CC	27	6	0.825	0.245–2.786	1.000
Yes	TT	25	9	1.337	0.432–4.141	0.776
	TC+CC	19	16	3.128	1.076–9.095	0.042*
	rs2481084					
No	TT	30	7	Reference		
	TC+CC	23	6	1.118	0.331–3.781	1.000
Yes	TT	28	13	1.990	0.694–5.707	0.299
	TC+CC	16	12	3.214	1.057–9.778	0.054

Note: *$p<0.05$.

TABLE 5 Stratified analysis: type 2 diabetes mellitus (DM).

DM		Control	CSVD	*OR*	95%*CI*	*p*
	rs790056					
No	TT	40	10	Reference		
	TC+CC	40	15	1.500	0.602–3.736	0.492
Yes	TT	11	6	2.182	0.649–7.336	0.209
	TC+CC	6	7	4.667	1.282–16.990	0.031*
	rs2481084					
No	TT	47	13	Reference		
	TC+CC	33	12	1.315	0.533–3.241	0.645
Yes	TT	11	7	2.301	0.744–7.119	0.217
	TC+CC	6	6	3.615	0.997–13.110	0.069

Note: *$p<0.05$

As far as we are aware, expression of JAM-A at the BBB has not been studied previously and our study is the first to examine an association between JAM-A polymorphism and VaD.

Having a slightly older age group as controls may mean we are more confident that these participants are truly negative for cognitive impairment as they are subjected to longer periods of adverse cerebrovascular risk factors (if present) and therefore are less likely to be false-negative controls when compared to the situation if controls were to be younger than or equal to the age of VaD patients.

However, there are limitations to the findings of our study. The population of our CSVD sample is small. Hence, the sample may not have adequate power to detect small differences as illustrated when genotypes of rs2481084 were analyzed with hyperlipidemia (OR = 3.210, $p = 0.054$) and with diabetes (OR = 3.620, $p = 0.069$) when CSVD patients were compared to controls (p values just eclipsed 0.050 threshold).

Nevertheless, our study may serve as a pilot for bigger studies that may prove genetic polymorphisms of tight junctions of blood brain barrier when they interact with vascular risk factors (diabetes, hypertension, or hyperlipidaemia) may pose additional burden as risk factors for CSVD.

AUTHOR CONTRIBUTIONS

D. K. Y. Chan conceptualized and contributed to writing the paper. Data collection and writing was done by P. X., K. K., S.C., N.B. conducted laboratory work; E. K. W. C contributed to writing; Y. H. X performed data analysis.

ACKNOWLEDGMENTS

Not applicable.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

Daniel Chan is the Editorial Board member of Aging Medicine and one of the co-authors of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. Other authors have nothing to disclose.

ETHICS STATEMENT

Ethics was obtained from South Western Sydney Local Health District Human Research Ethics Committee (HREC/16/LPOOL/199).

ORCID

Nady Braidy https://orcid.org/0000-0002-0497-5572
Daniel K. Y. Chan https://orcid.org/0000-0003-0481-3933

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How to cite this article: Xie P, Kancherla K, Chandramohan S, et al. Involvement of single nucleotide polymorphisms of junction adhesion molecule with small vessel vascular dementia. *Aging Med*. 2023;6:347-352. doi:10.1002/agm2.12278