

Sex-Based Differences in Disease Burden and Phenotype in CADASIL

A Multicenter Study of 368 Korean Patients

Joong-Goo Kim,¹ Jay Chol Choi,¹ Chul-Hoo Kang,¹ Jung-Hwan Oh,¹ Jung Seok Lee,¹ Ji-Hoon Kang,¹ Sukyung Byeon,¹ Jae-Sung Lim,² Bum Joon Kim,² Hyunjin Kim,² Chong Hyun Suh,³ Sung Hyuk Heo,⁴ Ho Geol Woo,⁴ Hyo Suk Nam,⁵ Byung-Chul Lee,⁶ Kyung-Ho Yu,⁶ Mi Sun Oh,⁶ Minwoo Lee⁶ et al.

Correspondence
Prof. Choi
jaychoi@jejunu.ac.kr

Neurol Genet 2026;12:e200353. doi:10.1212/NXG.0000000000200353

Abstract

Background and Objectives

Previous studies have reported mixed findings regarding sex differences in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), with some indicating earlier ischemic events in men, whereas others found no significant difference in stroke onset. However, evidence from Asian populations remains limited, where clinical manifestations and *NOTCH3* variant distribution differ substantially from those in European cohorts. We investigated sex-specific variations in clinical phenotypes and brain MRI characteristics among Korean patients with CADASIL.

Methods

In this nationwide retrospective study, 577 patients were screened for CADASIL across 26 centers in South Korea. After excluding those with benign or uncertain variants or insufficient clinical or MRI data, 368 individuals with pathogenic *NOTCH3* variants were included in the final analysis. Clinical features, vascular risk factors, and *NOTCH3* variant positions classified by epidermal growth factor–like repeat (EGFr) domains were compared between sexes. Brain MRI findings—including white matter hyperintensities (WMHs), lacunes, cerebral microbleeds, and atrophy—were evaluated. Sex differences in the onset of ischemic stroke and dementia were analyzed using Kaplan-Meier and Cox proportional hazards models.

Results

The mean age of the patients at data collection was 61.7 ± 11.9 years, and 48.6% were male. Thirty-six distinct pathogenic variants were identified. The most frequent variant was R544C (40.8%) located at the EGFr 13/14 interdomain boundary (corresponding to exon 11). Other recurrent variants were R75P (17.9%), C542R (5.4%), and R587C (4.6%). Men exhibited a higher prevalence of ischemic stroke (70.9% vs 44.4%, $p < 0.001$) and experienced their first event at an earlier age (median 53 vs 59 years, log-rank $p < 0.001$). On brain MRI, male sex was independently associated with a greater lacune burden (odds ratio 3.03, 95% CI 1.70–5.38, $p < 0.001$) while female sex tended to show higher WMH volume.

Discussion

This nationwide study highlights distinct sex differences in CADASIL presentation within a Korean population. Male patients exhibited a higher prevalence and earlier onset of ischemic stroke not fully explained by conventional vascular risk factors. These findings underscore the importance of integrating sex, hormonal, and genetic-epigenetic factors into future research to guide precision phenotyping and sex-informed clinical management in CADASIL.

The Author Byline is continued at the end of the article.

Author affiliations appear at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2026 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

e200353(1)

MORE ONLINE

Supplementary Material

Glossary

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **CMB** = cerebral microbleed; **CSVD** = cerebral small vessel disease; **EGFr** = epidermal growth factor-like repeat; **ICH** = intracerebral hemorrhage; **K-MMSE** = Korean Mini-Mental State Examination; **mRS** = modified Rankin Scale; **SNSB** = Seoul Neuropsychological Screening Battery; **TIA** = transient ischemic attack; **VUS** = variant of uncertain significance; **WMHs** = white matter hyperintensities.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common monogenic form of small vessel disease, caused by pathogenic variants in the *NOTCH3* gene, typically affecting the extracellular domain of the encoded receptor.^{1,2} The disease is characterized by recurrent strokes, cognitive decline, migraine, and psychiatric symptoms.³ Increasing evidence suggests that sex plays a crucial role in its clinical presentation and progression.⁴⁻¹⁰ Previous studies have indicated that male patients with CADASIL tend to experience a more aggressive disease course, characterized by a higher risk of stroke, dementia, disability, and shorter survival compared with female patients.^{4,6,8-10} For instance, a retrospective study of 411 patients with CADASIL found that men had a significantly lower median age at death (64.6 years) than women (70.7 years) and became bedridden at an earlier age.⁸ In addition, male patients had an approximately twofold higher risk of stroke and dementia compared with female patients after adjustment for age, *NOTCH3* variant position, and other vascular risk factors.^{4,9} However, some studies did not find significant sex differences in the age at stroke onset, whereas others reported a trend toward earlier ischemic events in men.^{5,6,8} Conversely, female patients showed a higher prevalence of migraine with aura.⁵

Although these findings provide valuable insights into sex-related differences in CADASIL, a comprehensive understanding of these differences remains incomplete. Most prior studies were conducted in European cohorts, and their results regarding stroke onset and disease burden have been inconsistent. Moreover, little is known about these patterns in Asian populations, where CADASIL appears to present with later disease onset, more frequent cerebral microbleeds (CMBs) and intracerebral hemorrhage (ICH), and distinctive *NOTCH3* variants such as R75P and R544C.¹¹⁻¹³ Therefore, the aim of this study was to elucidate sex-specific variations in the clinical manifestations and neuroimaging characteristics of Korean patients with CADASIL, thereby addressing a critical gap in our understanding of sex-related disease expression across different ethnic backgrounds.

Methods

Study Design and Participants

In this Korean nationwide retrospective CADASIL study, patients aged 19 years or older who were either confirmed or suspected of having CADASIL through genetic testing were

enrolled from 26 nationwide institutions in South Korea (eFigure 1). Screened participants included individuals identified with a pathogenic, likely pathogenic, or variant of uncertain significance (VUS) in the *NOTCH3* gene. The study period covered patients tested between January 1, 2013, and December 31, 2023, and data were collected from medical records through July 31, 2024. Patients were excluded if their clinical, genetic, or brain MRI data could not be sufficiently assessed from medical records. Variant classification was performed according to the ClinVar database as of November 30, 2024.¹⁴

Data Collection

The collected data encompassed (1) demographic information such as age, sex, height, weight, and educational background, as well as family history, including stroke, dementia, depression, and migraine; (2) genetic test results detailing the location of genetic variants and amino acid changes; (3) clinical symptoms and their onset age, such as stroke (ischemic, hemorrhagic), cognitive impairment, dementia, recurrent headaches, parkinsonism, and epilepsy; (4) vascular risk factors—including hypertension, diabetes, hyperlipidemia, smoking, alcohol intake, and atrial fibrillation; (5) information on medications for hypertension, hyperlipidemia, diabetes, antithrombotic therapy, and dementia treatment; (6) brain MRI along with laboratory assessments such as blood tests and blood pressure, pulse rate, and ECG results; and (7) cognitive and disability test results, including modified Rankin Scale (mRS) score,¹⁵ Korean Mini-Mental State Examination (K-MMSE),¹⁶ and the Seoul Neuropsychological Screening Battery (SNSB).^{17,18} We used the raw K-MMSE score and z-scores for 5 cognitive domains (attention, language, visuospatial functions, memory, and frontal/executive functions) from the SNSB test for the analyses.

Definition of Clinical Outcomes and Covariates

Clinical outcomes included ischemic stroke (including transient ischemic attack [TIA]), intracerebral hemorrhage, recurrent headache, cognitive impairment or dementia, parkinsonism, and epilepsy. Ischemic stroke, including TIA, was defined as a sudden focal neurologic deficit attributable to a vascular cause, lasting more than 24 hours with corresponding acute infarction on diffusion-weighted MRI or equivalent radiologic evidence, or lasting less than 24 hours without radiologic evidence of infarction (TIA), according to the AHA/ASA diagnostic criteria.¹⁹ ICH was identified when focal neurologic symptoms or signs were associated with

parenchymal bleeding confirmed on neuroimaging. Recurrent headaches were defined as a physician-diagnosed history of recurrent headache documented in the medical records, based on at least 2 separate headache episodes. In this study, recurrent headaches were included as one of the manifestations of CADASIL symptoms rather than classified as migraine, because previous studies have reported that migraine was found in only a minority of Korean CADASIL patients with R544C, with other headaches classified as tension-type or unclassifiable.²⁰ Cognitive impairment was defined as a Clinical Dementia Rating (CDR) score of 0.5, and dementia was defined as a CDR score of 1 or higher.²¹ Parkinsonism and epilepsy were identified based on clinical documentation by the treating physicians at each participating center.

Covariates included age, sex, variant location (epidermal growth factor-like repeat [EGFr] 1–6 vs 7–34), and vascular risk factors. Age was defined as the chronological age at the time of data abstraction in 2023 and used as the baseline demographic variable rather than age at onset or diagnosis. Vascular risk factors were defined according to standard clinical guidelines. Hypertension was identified by a documented diagnosis, antihypertensive medication use, or repeated blood pressure measurements showing systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg. Diabetes mellitus was defined by medical documentation, fasting plasma glucose ≥ 126 mg/dL, HbA1c $\geq 6.5\%$, or treatment with glucose-lowering agents. Hyperlipidemia was defined by total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/dL, or lipid-lowering therapy. Smoking was defined as having a current or past history of cigarette smoking. Alcohol intake was defined as a documented history of regular drinking in the medical records.

Follow-Up

The follow-up period was defined as the time from the patient's first visit to the participating center for CADASIL-related symptoms to the date of the last recorded clinical visit, including death when applicable. Follow-up data were available for 347 of the 368 patients (94.3%), excluding 21 patients who lacked longitudinal clinical information.

Brain MRI Analysis

In this study, the collection and analysis of brain MRI data were led by JS Lim and CH Suh from Asan Medical Center. Participating institutions anonymized all DICOM headers before transmitting MRI data. MRI analysis was conducted in accordance with the STRIVE (Standards for Reporting Vascular Change Neuroimaging) criteria.²² Brain MRI scans were rated for white matter hyperintensities (WMHs), lacunes, CMBs, dilated perivascular space (dPVS), and brain atrophy according to the CADA-MRIT criteria.²³ All ratings were performed by the same neuroradiologist (CH Suh, 14 years of clinical experience in neuroradiology). We also assessed the presence of WMHs on anterior temporal lobe and external capsule, which are frequently seen in patients with CADASIL.²⁴ In addition, brain volume and WMH volume were measured by using commercialized, automated software using

deep learning (VUNO Med-DeepBrain, Seoul, South Korea), and normalized WMH volume (nWMHv) was calculated.^{25,26}

In this retrospective study, we collected all brain MRI scans conducted during the study period. Therefore, many patients had multiple brain MRI scans. From these MRI scans, we first selected those obtained closest to the diagnosis date and containing the greatest number of sequences to assess WMHs, lacunes, CMBs, and brain atrophy. Second, we selected brain MRI scans that best allowed for the evaluation of WMHs, lacunes, CMBs, or brain atrophy, even if they were examined on different dates. The second MRI selection was used for sensitivity analysis.

Statistical Analysis

Continuous variables were summarized as means with standard deviations or median with interquartile range and compared between sexes using independent *t* tests or Mann-Whitney U tests, as appropriate. Categorical variables were presented as frequencies with percentages and analyzed using chi-square or Fisher exact tests. Multivariable logistic regression was performed to assess associations between sex and clinical manifestations including ischemic stroke, ICH, and dementia, adjusting for age, vascular risk factors, and *NOTCH3* variant position. For recurrent headaches, only age and *NOTCH3* variant position were adjusted. Kaplan-Meier survival analysis with log-rank tests evaluated sex differences in the onset of ischemic stroke, ICH, recurrent headaches, and dementia. In this retrospective study, patients who were lost to follow-up were considered censored at their last follow-up date. Cox proportional hazards models were applied to estimate hazard ratios for these outcomes. Ordinal logistic regression was used to examine the associations between age, vascular risk factors, and *NOTCH3* variant position with markers of cerebral small vessel diseases, except for nWMHv, which was analyzed using linear regression. Sensitivity analyses were conducted using the second MRI data set to confirm robustness. A significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata data analysis software (Version 18, StataCorp, College Station, TX).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Board (IRB) of Jeju National University Hospital (IRB No. 2023-08-012) and the respective IRBs of all participating institutions prior to initiating the study. This study was conducted retrospectively using data obtained during routine clinical practice. The requirement for informed consent was waived by the institutional review board because of the use of deidentified data and the minimal risk to participants.

Data Availability

The data sets generated and/or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Results

Demographic Characteristics

A total of 577 patients were screened for CADASIL in this study. After excluding those with a diagnosis before January 1, 2013 ($n = 59$), insufficient clinical information ($n = 50$), unavailable genetic test results ($n = 5$), or missing brain MRI ($n = 18$), 445 patients were eligible for inclusion. Among these, 368 (82.7%) carried pathogenic or likely pathogenic variants, 46 (10.3%) had VUS, and 31 (7.0%) had benign variants (eFigure 2). The final analyses were performed on the 368 patients with pathogenic or likely pathogenic *NOTCH3* variants.

The mean age of the patients at the data collection was 61.7 ± 11.9 years, and 48.6% were male. Men ($n = 179$) were significantly younger than women ($n = 189$) (59.1 ± 11.2 vs 64.2 ± 12.1 years, $p < 0.001$). Men had a significantly higher prevalence of diabetes mellitus (25.7% vs 12.7%, $p = 0.001$), smoking (56.1% vs 3.6%, $p < 0.001$), and alcohol consumption (45.2% vs 13.3%, $p < 0.001$) (Table 1). The median follow-up duration was 45 months (interquartile range, 17–83 months).

Genetics

Regarding genetics, patients harbored 36 distinct pathogenic variants. The most frequent variant was R544C (40.8%), which was located at the EGFr 13/14 interdomain boundary (corresponding to exon 11) (Figure 1 and eTable 1). Other recurrent variants included R75P (17.9%), C542R (5.4%), and R587C (4.6%). Notably, a disproportionately high number of patients with CADASIL (approximately 24.7% of the cohort) were identified from Jeju Island, far exceeding what would be expected based on its population size. Cysteine-altering variants were identified in 80.7% of patients; in one-third of patients, the variant was located in EGFr 1–6 (33.2%). There were no significant differences in the distribution of *NOTCH3* variant positions between men and women. EGFr 1–6 variants were present in 35.8% of men and 30.7% of women ($p = 0.302$). Cysteine-altering variants were similarly prevalent in both sexes (79.9% vs 81.5%, $p = 0.699$).

Clinical Manifestations

Ischemic stroke was the most common clinical manifestation, occurring in 57.3% of patients, followed by recurrent headaches (26.4%), dementia (16.6%), psychiatric symptoms (14.7%), ICH (9.5%), parkinsonism (7.6%), and seizures (4.6%). Men had a higher prevalence of ischemic stroke than women (70.9% vs 44.4%, $p < 0.001$), whereas women were more likely to report recurrent headaches (35.4% vs 16.9%, $p < 0.001$). Dementia was observed more frequently in women (19.6% vs 13.4%), although the difference was not statistically significant ($p = 0.117$). Male sex (odds ratio [OR]: 4.01, 95% CI 2.16–7.43, $p < 0.001$) remained significantly associated with an increased risk of ischemic stroke, along with variant position on EGFr 1–6 (OR: 2.11, 95% CI 1.22–3.66, $p = 0.007$) and hypertension (OR: 1.86, 95% CI

1.10–3.16, $p = 0.021$) on multivariable analysis. Male sex was associated with a significantly decreased risk of recurrent headache on multivariable analysis (OR: 0.32, 95% CI 0.19–0.53, $p < 0.001$) (Figure 2). When we stratified the regression models by hypertension or smoking status, the ORs for ischemic stroke associated with male sex were increased further in the subgroup without hypertension (OR: 5.08, 95% CI 2.31–11.20, $p < 0.001$) compared with the subgroup with hypertension (OR: 3.00, 95% CI 1.01–8.94, $p = 0.048$) and also in the subgroup without smoking (OR: 4.83, 95% CI 2.42–9.62, $p < 0.001$) compared with the subgroup with smoking (OR: 1.70, 95% CI 0.27–10.66, $p = 0.573$), suggesting an independent association between male sex and increased risk of ischemic stroke regardless of hypertension or smoking (eFigure 3).

Age at Onset of Clinical Symptoms

The median age at onset of ischemic stroke was 56 years (interquartile range, 47 to 63) while the median ages at onset of ICH, recurrent headaches, and dementia were 54 (46–65), 75 (68–80), and 51 (40–59) years, respectively. Kaplan-Meier analysis demonstrated a significantly shorter ischemic stroke-free survival in male patients compared with female patients (log-rank $p < 0.001$; median age at first-ever ischemic stroke: 53 years in men vs 59 years in women). Male sex (HR: 2.78, 95% CI 1.92–4.03, $p < 0.001$) and EGFr 1–6 (HR: 2.09, 95% CI 1.51–2.89, $p < 0.001$) were significantly associated with earlier onset of ischemic stroke on Cox proportional hazard analysis, while male sex was associated with significantly later onset of recurrent headache (HR: 0.59, 95% CI 0.38–0.90, $p = 0.016$) (Table 2). In subgroup analyses by hypertension status, male sex was associated with a higher risk of earlier onset of stroke in the subgroup without hypertension (HR: 3.06, 95% CI 1.90–4.94, $p < 0.001$) than in the subgroup with hypertension (HR: 2.55, 95% CI 1.39–4.69, $p = 0.003$), suggesting an independent association between earlier onset of ischemic stroke and male sex (eFigure 4). No significant sex differences were observed for ICH (HR: 2.03, 95% CI 0.80–5.18, $p = 0.136$) or dementia (HR: 1.26, 95% CI 0.56–2.84, $p = 0.579$) (Table 2 and Figure 3).

Disability and Cognitive Function Tests

The mRS score, K-MMSE score, and SNSB domain test results were available for 176, 174, and 96 patients, respectively. The mean age at the time of mRS and K-MMSE examinations did not differ between male and female patients (53.7 ± 3.0 years vs 53.4 ± 3.1 years for mRS; 54.2 ± 3.0 years vs 53.5 ± 3.0 years for K-MMSE). However, the mean age at the SNSB examination was slightly greater for male patients compared with female patients (54.7 ± 2.8 years vs 53.5 ± 2.9 years, $p = 0.020$). There were no significant sex differences in the mRS or K-MMSE score. Of 5 cognitive domains assessed with the SNSB test, only the z-scores of frontal/executive functions scores were significantly lower in men than in women (median with interquartile range, -1.81 [-4.14 to -0.56] vs -1.28 [-2.54 to -0.06], $p = 0.022$).

Table 1 Characteristics of the Patients by Sex

	Men (N = 179)	Women (N = 189)	Total (N = 368)	<i>p</i> Value
Age (y)	59.1 (11.2)	64.2 (12.1)	61.7 (11.9)	<0.001
Vascular risk factors				
Hypertension	81 (45.3)	81 (42.9)	162 (44.0)	0.644
Diabetes mellitus	46 (25.7)	24 (12.7)	70 (19.0)	0.001
Hypercholesterolemia	87 (48.6)	90 (47.9)	177 (48.2)	0.889
Smoking	96 (56.1)	6 (3.6)	102 (30.0)	<0.001
Alcohol drinking	75 (45.2)	22 (13.3)	97 (29.2)	<0.001
Atrial fibrillation	3 (1.7)	1 (0.5)	4 (1.1)	0.296
Clinical manifestations				
Ischemic stroke	127 (70.9)	84 (44.4)	211 (57.3)	<0.001
ICH	18 (10.1)	17 (9.0)	35 (9.5)	0.741
Dementia	24 (13.5)	37 (19.6)	61 (16.6)	0.117
Recurrent headache	30 (16.9)	67 (35.4)	97 (26.4)	<0.001
Psychiatric	24 (13.4)	30 (15.9)	54 (14.7)	0.504
Parkinsonism	14 (7.8)	14 (7.4)	28 (7.6)	0.881
Seizure	9 (5.0)	8 (4.2)	17 (4.6)	0.716
Onset age, y				
Ischemic stroke	53 (46–60)	59 (52–68)	56 (47–63)	<0.001
ICH	46 (38–56)	58 (50–67)	54 (46–65)	0.149
Dementia	65 (62–74)	76 (72–80)	75 (68–80)	0.184
Recurrent headache	46 (39–54)	54 (46–63)	51 (40–59)	0.016
NOTCH3 variant				
EGFr position				
EGFr 1-6	64 (35.8)	58 (30.7)	122 (33.2)	0.302
EGFr 7-34	115 (64.2)	131 (69.3)	246 (66.8)	
Cysteine involvement				
Cys-sparing	36 (20.1)	35 (18.5)	71 (19.3)	0.699
Cys-altering	143 (79.9)	154 (81.5)	297 (80.7)	

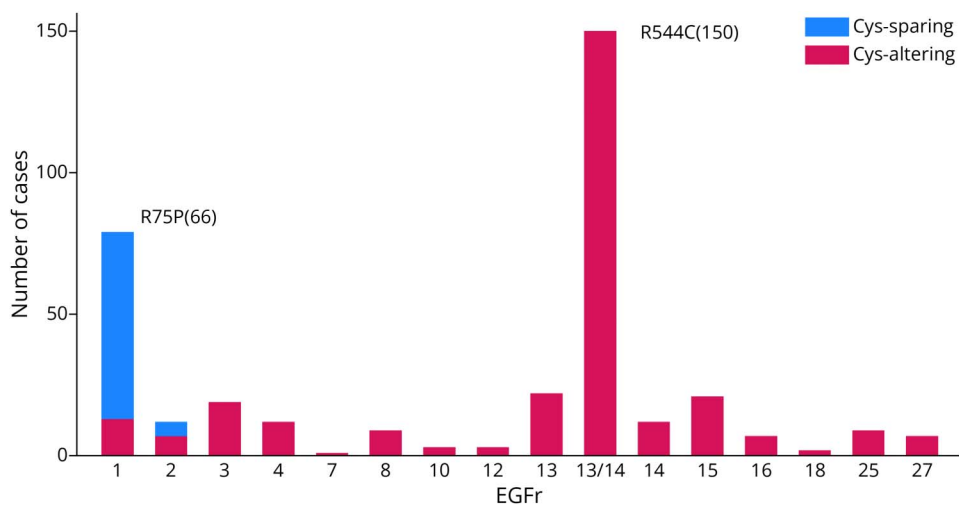
Abbreviations: AChEIs = acetylcholine esterase inhibitors; EGFr = epidermal growth factor-like repeat; ICH = intracerebral hemorrhage. Results are shown as n (%) or mean (SD). Onset ages are shown as median with interquartile range and *p* value for the log-rank test.

Brain MRI Findings

Brain MRI scans were available for 304 patients in the primary analysis data set. The mean age at brain MRI was 53.5 ± 3.2 years, with no difference between men and women (53.5 ± 3.1 years vs 53.5 ± 3.2 years, $p = 0.944$). Lacunes were present in 74.0% of patients, with 22.0% having more than 10 lacunes. CMBs were observed in 63.9% of patients, with 24.2% showing >10 (T2*)/ >20 (SWI) CMBs. The overall nWMHv was $3.9 \pm 2.2\%$ of total brain volume (eTable 2). Of various MRI features, men exhibited a significantly greater burden of

lacunes compared with women ($p < 0.001$) while women showed a significantly greater nWMHv compared with men ($3.6 \pm 2.1\%$ vs $4.2 \pm 2.3\%$, $p = 0.012$) in unadjusted analysis. Male sex was associated with a significantly increased risk of higher category of lacunes (OR 3.03, 95% CI 1.70–5.38, $p < 0.001$), along with age (OR 1.03, 95% CI 1.01–1.05, $p = 0.002$) and hypertension (OR 1.86, 95% CI 1.15–3.03, $p = 0.002$) in ordinal logistic regression analysis. However, female sex was not associated with greater nWMHv compared with male sex after adjusting for age, variant position, and vascular

Figure 1 Distribution of NOTCH3 Variants by EGFr Domain in 368 Korean Patients With CADASIL



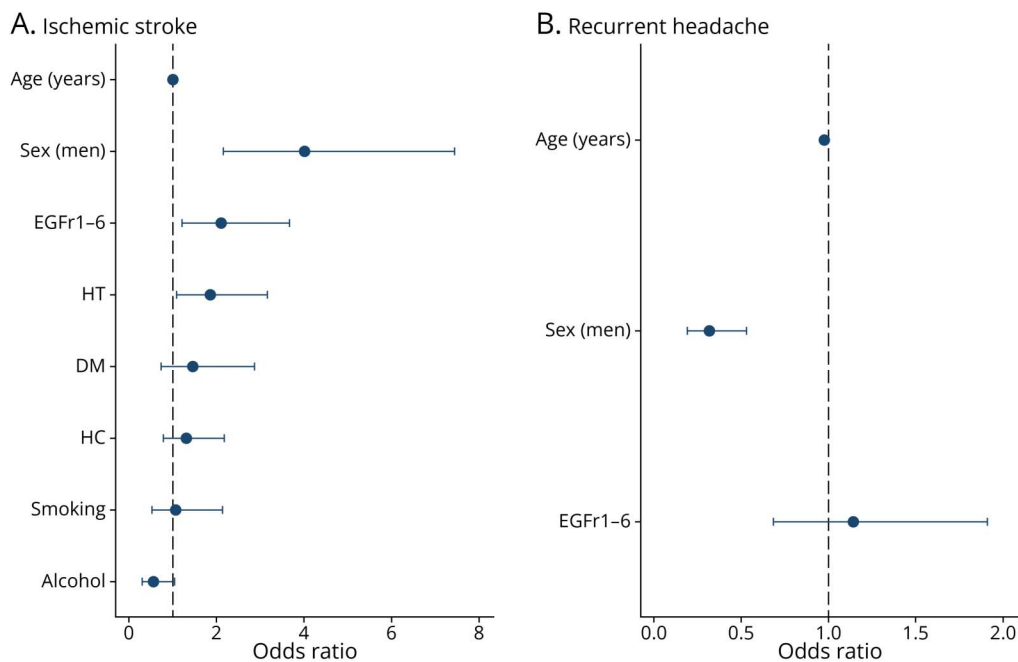
risk factors (Figure 4). The sensitivity analysis with the second set of brain MRI that contained scans from 332 patients showed similar results (eFigure 5 and eTable 3).

Discussion

Our findings align with prior European studies, suggesting that men with CADASIL have a higher risk of ischemic stroke and increased lacunes on brain MRI compared with women.^{4,5,9}

However, some studies did not find significant sex differences in stroke onset while others reported a trend toward earlier ischemic events in men, consistent with our results.^{5,6,8} Notably, the higher risk of ischemic stroke and its earlier onset in men could not be explained by concurrent hypertension or smoking as the risk seems to be greater in the subgroups without hypertension or smoking. In addition, our study confirms the previously observed association between female sex and a higher prevalence of headaches.⁵ These findings reinforce

Figure 2 Factors Associated With Ischemic Stroke and Recurrent Headache on Multivariable Analyses



DM = diabetes mellitus; HC = hypercholesterolemia; HT = hypertension.

Table 2 Factors Affecting Onset of Ischemic Stroke, Intracerebral Hemorrhage, Dementia, and Recurrent Headache

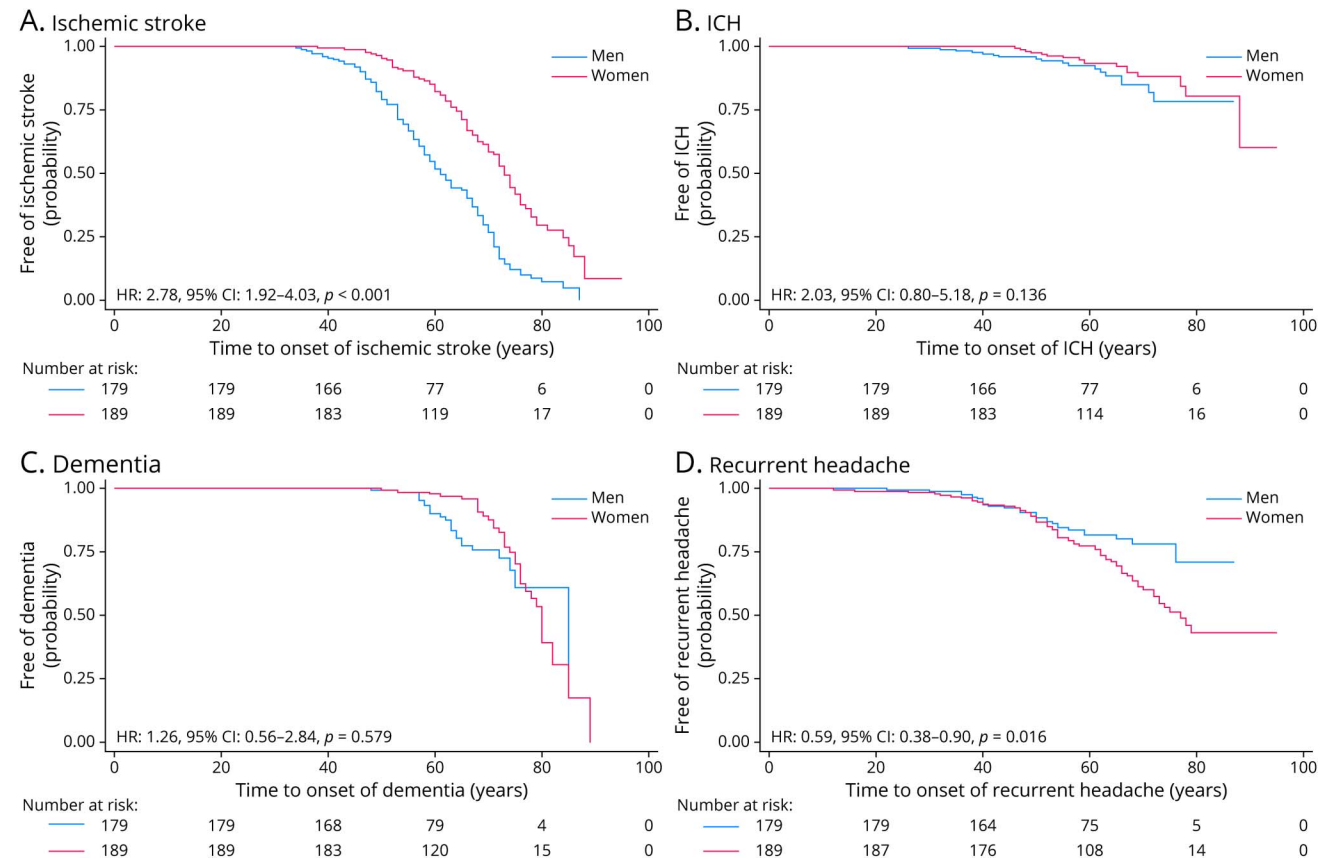
	Ischemic stroke			ICH			Dementia			Recurrent headache		
	Hazard ratio	95% CI	p Value	Hazard ratio	95% CI	p Value	Hazard ratio	95% CI	p Value	Hazard ratio	95% CI	p Value
Male sex	2.78	1.92–4.03	<0.001	2.03	0.80–5.18	0.136	1.26	0.56–2.84	0.579	0.59	0.38–0.90	0.016
EGFr 1–6	2.09	1.51–2.89	<0.001	1.40	0.60–3.26	0.437	0.96	0.44–2.07	0.909	1.50	0.99–2.28	0.058
Hypertension	1.30	0.94–1.79	0.108	1.92	0.86–4.28	0.112	0.95	0.51–1.76	0.867	—	—	—
Diabetes	0.97	0.67–1.41	0.877	0.42	0.14–1.30	0.134	0.98	0.47–2.07	0.965	—	—	—
Hypercholesterolemia	0.91	0.67–1.24	0.567	1.15	0.54–2.45	0.721	1.11	0.60–2.05	0.750	—	—	—
Smoking	0.90	0.62–1.29	0.556	0.64	0.24–1.69	0.367	1.02	0.42–2.46	0.958	—	—	—
Alcohol drinking	1.00	0.71–1.41	0.996	1.59	0.67–3.78	0.292	0.97	0.44–2.18	0.950	—	—	—

Abbreviations: CI = confidence interval; EGFr = epidermal growth factor-like repeat; ICH = intracerebral hemorrhage.

the importance of considering sex as a biological variable in CADASIL prognosis and management.

Sex differences in cerebral small vessel disease (CSVD) have been increasingly recognized, with distinct patterns in onset age and imaging features. Men tend to experience CSVD-

related ischemic events, including lacunar stroke, at younger ages.^{27–29} By contrast, women often show greater burden of WMH in late life, potentially due to loss of estrogen-mediated vascular protection after menopause.^{30,31} Neuroimaging studies have shown that men have a higher prevalence of lacunes and CMBs at a given age,²⁸ whereas women, despite

Figure 3 Sex Differences in Kaplan-Meier Estimates

For the onset of ischemic stroke (A), intracerebral hemorrhage (B), dementia (C), and recurrent headache (D).

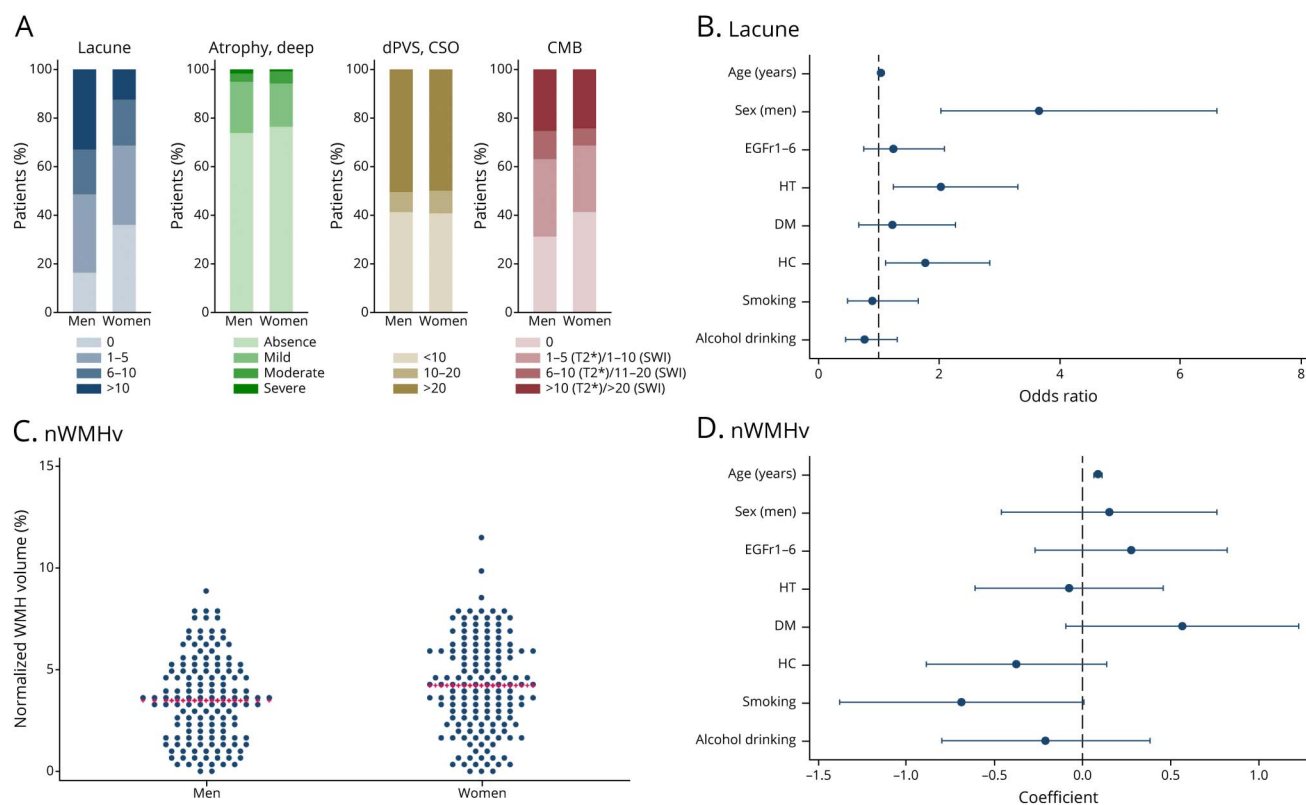
initially lower lesion burden, may exhibit faster progression of WMHs and CMBs once CSVD is established.^{32,33} In CADASIL, our findings reflect this sex-specific pattern: male patients exhibited earlier onset of ischemic stroke and a greater lacune burden while female patients tend to show greater WMH volume. However, the WMH volume difference did not remain significant after adjustment for age, variant position, and vascular risk factors. A previous study has shown that WMH burden increases more steeply with advancing age in postmenopausal women.³¹ Therefore, the absence of a significant sex difference in adjusted analyses likely reflects that most female participants were scanned before the age at which WMH accumulation accelerates in this study. Taken together, these observations highlight the role of sex in modulating both the clinical expression and radiologic burden of CADASIL, suggesting underlying differences in pathophysiology, hormonal milieu, and vulnerability to vascular injury.

Several biological mechanisms may account for these sex-related disparities. First, estrogen and other sex hormones play key roles in cerebrovascular homeostasis through effects on endothelial nitric oxide production, vasodilation, and neuroprotection.³⁴ Estrogen has been shown to enhance small vessel

function and maintain cerebral blood flow, while its decline after menopause may accelerate vascular injury and increase WMH volumes.³⁵ By contrast, androgen exposure has been linked to increased vascular tone and proinflammatory responses that could contribute to the higher ischemic burden observed in men.³⁶

Beyond hormonal influences, genetic and epigenetic factors are increasingly recognized as contributors to sex-related differences in vascular disease, including CADASIL. Research on CADASIL heritability has shown that factors beyond the *NOTCH3* variant substantially influence disease expression. A study of 151 patients from 95 families demonstrated that T2 lesion volume on MRI is highly heritable, with additive genetic factors accounting for approximately 63–74% of its variance beyond the effect of the causative *NOTCH3* variant.³⁷ These findings suggest that individual genetic backgrounds and modifier loci play a critical role in determining disease severity and imaging phenotype, even among carriers of the same pathogenic variant. Recent investigations have further demonstrated that sex-specific genetic and epigenetic regulation contributes to vascular differences. Studies have reported that variation in endothelial function, lipid metabolism, and vascular remodeling

Figure 4 Sex Differences in Cerebral Small Vessel Disease Markers on Brain MRI Findings



(A) Distribution of lacunes, deep brain atrophy, dilated perivascular spaces (dPVSs) in the centrum semiovale (CSO), and cerebral microbleeds (CMBs) by sex. (B) Odds ratios for the severity of lacunes. (C) Distribution of white matter hyperintensity (WMH) volume percentages by sex; the horizontal red line indicates median value. (D) Odds ratios for the WMH volume percentages. DM = diabetes mellitus; HC = hypercholesterolemia; HT = hypertension.

arises from differential genetic and epigenetic modulation between sexes, and that X-chromosome dosage imbalance, escape from X-inactivation, and sex-biased gene expression patterns influence cardiovascular phenotypes.^{38,39} Collectively, these findings indicate that male and female genomes respond differently to vascular stressors and inflammatory signaling, potentially interacting with *NOTCH3*-related pathways to produce distinct small vessel injury trajectories in CADASIL.

An intriguing feature of our cohort was the marked geographic clustering of CADASIL cases in Jeju Island, which accounted for nearly one-quarter of all patients despite representing only approximately 1% of the Korean population. This striking concentration suggests a regional founder effect, likely driven by the R544C variant, which constituted 40.8% of all pathogenic variants in our study. Previous studies have shown that over 90% of CADASIL cases identified in Jeju carry this same substitution, which has been associated with distinct clinical and neuroimaging phenotypes—such as a higher frequency of ICH, fewer migraine manifestations, and relatively lower anterior temporal lobe involvement compared with European cohorts.^{20,40} The R544C variant accounted for 90.3%, 70.5%, and 15.5% of CADASIL pedigrees in Jeju Island, Taiwan, and southeastern China, respectively, with shared haplotypes among Taiwanese and Fujian patients supporting descent from a common ancestor and a shared East Asian founder origin.^{41,42} Comparable founder genetic variants have been described for R133C in Finland and Kyushu, Japan, underscoring that geographically restricted *NOTCH3* variants contribute to regional clustering and population-specific phenotypic patterns of CADASIL.^{43,44}

Despite its strengths, this study has several limitations. First, as a retrospective multicenter analysis, it is subject to potential selection bias and inconsistencies in data collection across participating centers. The relatively high frequency of stroke and other cerebrovascular manifestations observed in our cohort likely reflects both the older age distribution of participants at the time of data abstraction and the tertiary-care recruitment setting, where patients are more often referred after cerebrovascular events. Consequently, symptomatic individuals may have been overrepresented compared with the general CADASIL population. This inclusion bias should, therefore, be considered when interpreting the reported prevalence of clinical and imaging features, as the high proportion of stroke cases may partially reflect referral and selection bias rather than a true population-level difference in stroke susceptibility. Second, while brain MRI evaluations were standardized, differences in MRI protocols among institutions may have influenced quantitative imaging measurements. Third, although we adjusted for major vascular risk factors, unmeasured confounders, such as hormonal influences and lifestyle factors, might have contributed to the observed sex differences. Fourth, cognitive assessments were not detailed in this study because of limited number of patients being examined in this retrospective study. This limits our

ability to fully explore sex differences in cognitive impairment in patients with CADASIL. Finally, our genotype-phenotype analyses were based on the conventional dichotomization of *NOTCH3* variant locations into EGFr 1–6 vs EGFr 7–34 domains. Although recent evidence suggests that certain variants—particularly those in EGFr 8, 11, and 26—may also confer higher disease severity, the number of patients carrying these variants in our cohort was very small ($n = 9$, 2.5%).⁴⁵ Therefore, an additional subgroup analysis incorporating these domains would have been statistically underpowered and unlikely to yield robust conclusions. Future prospective studies with larger sample sizes and longitudinal follow-ups are needed to further validate these findings and explore biological mechanisms underlying sex differences.

In conclusion, this study is one of the largest to investigate sex differences in CADASIL within an Asian population, highlighting potential ethnic variations in disease expression. Male patients exhibited a higher prevalence and earlier onset of ischemic stroke that were not fully explained by conventional vascular risk factors, suggesting possible sex-intrinsic mechanisms underlying vascular injury. Variations in endothelial function and inflammatory signaling—modulated by both sex hormones and differential gene regulation—may shape distinct patterns of ischemic vulnerability and white matter injury between men and women. Understanding the interplay between hormonal, genetic, and epigenetic determinants of cerebrovascular vulnerability will be crucial for developing sex-informed monitoring and preventive strategies in CADASIL, particularly in the absence of curative therapies.

Author Byline (Continued)

Chi Kyung Kim,⁷ Kyungmi Oh,⁷ Sung Hoon Kang,⁷ Keon-Joo Lee,⁷ Jung Hoon Han,⁷ Young Seo Kim,⁸ Hyun Y. Kim,⁸ Hee-Jin Kim,⁸ Hee-Joon Bae,⁹ Moon-Ku Han,⁹ Jihoon Kang,⁹ Beom Joon Kim,⁹ Jun Yup Kim,⁹ Seung-Hoon Lee,¹⁰ Keun-Hwa Jung,¹⁰ Sung-Il Sohn,¹¹ Jeong-Ho Hong,¹¹ Hyungjong Park,¹¹ Jee-Hyun Kwon,¹² Wook-Joo Kim,¹² Dong-Ick Shin,¹³ Kyu Sun Yum,¹³ Hee-Yun Chae,¹³ Sang Min Sung,¹⁴ Sang Won Seo,¹⁵ Jun Pyo Kim,¹⁵ Jin-Man Jung,¹⁶ Kyungbok Lee,¹⁷ Tai Hwan Park,¹⁸ Sang-Soon Park,¹⁸ Jin Kyo Choi,¹⁸ Man Seok Park,¹⁹ Joon-Tae Kim,¹⁹ Kang-Ho Choi,¹⁹ Jae-Kwan Cha,²⁰ Dae-Hyun Kim,²⁰ Byeol-A Yoon,²⁰ Soo Joo Lee,²¹ Jae Guk Kim,²¹ Do-Hyung Kim,²¹ Dong-Eog Kim,²² Dong-Seok Gwak,²² Chulho Kim,²³ Sang-Hwa Lee,²³ Jun Lee,²⁴ Doo Hyuk Kwon,²⁴ Kyusik Kang,²⁵ Kwang-Yeol Park,²⁶ Hae-Bong Jeong,²⁶ Chan-Young Park,²⁶ Yong-Jin Cho,²⁷ Keun-Sik Hong,²⁷ Hong-Kyun Park²⁷

Affiliation

¹Department of Neurology, Jeju National University Hospital, Jeju National University College of Medicine, South Korea; ²Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; ³Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; ⁴Department of Neurology, Kyung Hee Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea; ⁵Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; ⁶Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, South Korea; ⁷Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea; ⁸Department of Neurology, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, South Korea; ⁹Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; ¹⁰Department of Neurology, Seoul National University Hospital, Seoul National

University College of Medicine, South Korea; ¹¹Department of Neurology, Keimyung University Dongsan Hospital, Keimyung University College of Medicine, Daegu, South Korea; ¹²Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, South Korea; ¹³Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, South Korea; ¹⁴Department of Neurology, Pusan National University Hospital, Pusan National University College of Medicine, Busan, South Korea; ¹⁵Department of Neurology, Samsung Medical Center, Sungkyunkwan University College of Medicine, Seoul, South Korea; ¹⁶Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, South Korea; ¹⁷Department of Neurology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, South Korea; ¹⁸Department of Neurology, Seoul Medical Center, South Korea; ¹⁹Department of Neurology, Chonnam National University Hospital, Chonnam National University College of Medicine, Gwangju, South Korea; ²⁰Department of Neurology, Dong-A University Hospital, Dong-A University College of Medicine, Busan, South Korea; ²¹Department of Neurology, Daejeon Eulji Medical Center, Eulji University College of Medicine, South Korea; ²²Department of Neurology, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, South Korea; ²³Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, South Korea; ²⁴Department of Neurology, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, South Korea; ²⁵Department of Neurology, Nowon Eulji Medical Center, Eulji University College of Medicine, Seoul, South Korea; ²⁶Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea; and ²⁷Department of Neurology, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, South Korea.

Author Contributions

J.-G. Kim: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J.C. Choi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C.-H. Kang: major role in the acquisition of data. J.-H. Oh: major role in the acquisition of data. J.S. Lee: major role in the acquisition of data. J.-H. Kang: major role in the acquisition of data. S. Byeon: major role in the acquisition of data. J.-S. Lim: major role in the acquisition of data. B.-J. Kim: major role in the acquisition of data. H. Kim: major role in the acquisition of data. C.H. Suh: major role in the acquisition of data; study concept or design; analysis or interpretation of data. S.H. Heo: major role in the acquisition of data. H.G. Woo: major role in the acquisition of data. H.S. Nam: major role in the acquisition of data. B.-C. Lee: major role in the acquisition of data. K.-H. Yu: major role in the acquisition of data. M.S. Oh: major role in the acquisition of data. M. Lee: major role in the acquisition of data. C.K. Kim: major role in the acquisition of data; study concept or design. K. Oh: major role in the acquisition of data. S.H. Kang: major role in the acquisition of data. K.-J. Lee: major role in the acquisition of data. J.H. Han: major role in the acquisition of data. Y.S. Kim: major role in the acquisition of data. H.Y. Kim: major role in the acquisition of data. H.-J. Kim: major role in the acquisition of data. H.-J. Bae: major role in the acquisition of data. M.-K. Han: major role in the acquisition of data. J. Kang: major role in the acquisition of data. B.J. Kim: major role in the acquisition of data. J.Y. Kim: major role in the acquisition of data. S.-H. Lee: major role in the acquisition of data. K.-H. Jung: major role in the acquisition of data. S.-I. Sohn: major role in the acquisition of data. J.-H. Hong: major role in the acquisition of data. H. Park: major role in the acquisition of data. J.-H. Kwon: major role in the acquisition of data. W.-J. Kim: major role in the acquisition of data. D.-I. Shin: major role in the acquisition of data. K.S. Yum: major role in the acquisition of data. H.-Y. Chae: major role in the acquisition of data. S.M. Sung: major role in the acquisition of

data. S.W. Seo: major role in the acquisition of data. J.P. Kim: major role in the acquisition of data. J.-M. Jung: major role in the acquisition of data. K. Lee: major role in the acquisition of data. T.H. Park: major role in the acquisition of data. S.-S. Park: major role in the acquisition of data. J.K. Choi: major role in the acquisition of data. M.S. Park: major role in the acquisition of data. J.-T. Kim: major role in the acquisition of data. K.-H. Choi: major role in the acquisition of data. J.-K. Cha: major role in the acquisition of data. D.-H. Kim: major role in the acquisition of data. B.-A. Yoon: major role in the acquisition of data. S.J. Lee: major role in the acquisition of data. J.G. Kim: major role in the acquisition of data. D.-H. Kim: major role in the acquisition of data. D.-E. Kim: major role in the acquisition of data. D.-S. Gwak: major role in the acquisition of data. C. Kim: major role in the acquisition of data. S.-H. Lee: major role in the acquisition of data. J. Lee: major role in the acquisition of data. D.H. Kwon: major role in the acquisition of data. K. Kang: major role in the acquisition of data. K.-Y. Park: major role in the acquisition of data. H.-B. Jeong: major role in the acquisition of data. C.-Y. Park: major role in the acquisition of data. Y.-J. Cho: major role in the acquisition of data. K.-S. Hong: major role in the acquisition of data. H.-K. Park: major role in the acquisition of data.

Study Funding

This work was supported by a research grant from Jeju National University Hospital in 2023.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Previously published in medRxiv (doi.org/10.1101/2025.04.28.25326613). Received by *Neurology® Genetics* July 10, 2025. Accepted in final form December 22, 2025. Submitted and externally peer-reviewed. The handling editor was Editor Peter B. Kang, MD, FAAN.

References

- Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383(6602):707-710. doi:10.1038/383707a0
- Choi JC. Genetics of cerebral small vessel disease. *J Stroke*. 2015;17(1):7-16. doi:10.5853/jos.2015.17.1.7
- Chabriet H, Joutel A, Dichgans M, Tournier-Lasserre E, Boussier MG. Cadasil. *Lancet Neurol*. 2009;8(7):643-653. doi:10.1016/S1474-4422(09)70127-9
- Dupe C, Guey S, Biard L, et al. Phenotypic variability in 446 CADASIL patients: impact of NOTCH3 gene mutation location in addition to the effects of age, sex and vascular risk factors. *J Cereb Blood Flow Metab*. 2023;43:153-166. doi:10.1177/0271678X221126280
- Gunda B, Hervé D, Godin O, et al. Effects of gender on the phenotype of CADASIL. *Stroke*. 2012;43(1):137-141. doi:10.1161/STROKEAHA.111.631028
- Hack RJ, Cerfontaine MN, Gravestijn G, et al. Effect of NOTCH3 EGF Receptor, sex, and cardiovascular risk factors on CADASIL clinical and neuroimaging outcomes. *Stroke*. 2022;53(10):3133-3144. doi:10.1161/STROKEAHA.122.039325
- Jia X, Ling C, Li Y, et al. Sex differences in frontotemporal atrophy in CADASIL revealed by 7-Tesla MRI. *Neuroimage Clin*. 2023;37:103298. doi:10.1016/j.nicl.2022.103298
- Opherk C, Peters N, Herzog J, Luedtke R, Dichgans M. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. *Brain*. 2004;127(Pt 11):2533-2539. doi:10.1093/brain/awh282
- Sukhonpanich N, Koohi F, Jolly AA, Markus HS. Changes in the prognosis of CADASIL over time: a 23-year study in 555 individuals. *J Neurol Neurosurg Psychiatry*. 2025;96(7):690-696. doi:10.1136/jnnp-2024-334823
- Pan AP, Potter T, Bako A, et al. Lifelong cerebrovascular disease burden among CADASIL patients: analysis from a global health research network. *Front Neurol*. 2023;14:1203985. doi:10.3389/fneur.2023.1203985

11. Liao YC, Hsiao CT, Fuh JL, et al. Characterization of CADASIL among the Han Chinese in Taiwan: distinct genotypic and phenotypic profiles. *PLoS One*. 2015; 10(8):e0136501. doi:10.1371/journal.pone.0136501
12. Min JY, Park SJ, Kang EJ, Hwang SY, Han SH. Mutation spectrum and genotype-phenotype correlations in 157 Korean CADASIL patients: a multicenter study. *Neurogenetics*. 2022;23(1):45-58. doi:10.1007/s10048-021-00674-1
13. Mukai M, Mizuta I, Watanabe-Hosomi A, et al. Genotype-phenotype correlations and effect of mutation location in Japanese CADASIL patients. *J Hum Genet*. 2020;65(8): 637-646. doi:10.1038/s10038-020-0751-9
14. ClinVar Database. *National Center for Biotechnology Information (NCBI)*. U.S. National Library of Medicine. Updated December 14, 2024. Accessed November 30, 2024. ncbi.nlm.nih.gov/clinvar/
15. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5): 604-607. doi:10.1161/01.str.19.5.604
16. Han C, Jo SA, Jo I, Kim E, Park MH, Kang Y. An adaptation of the Korean minimal state examination (K-MMSE) in elderly Koreans: demographic influence and population-based norms (the AGE study). *Arch Gerontol Geriatr*. 2008;47(3): 302-310. doi:10.1016/j.archger.2007.08.012
17. Ahn HJ, Chin J, Park A, et al. Seoul neuropsychological screening battery-dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci*. 2010;25(7):1071-1076. doi:10.3346/jkms.2010.25.7.1071
18. Ryu HJ, Yang DW. The Seoul neuropsychological screening battery (SNSB) for comprehensive neuropsychological assessment. *Dement Neurocogn Disord*. 2023;22: 1-15. doi:10.12779/dnd.2023.22.1.1
19. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276-2293. doi: 10.1161/STROKEAHA.108.192218
20. Choi JC, Song SK, Lee JS, Kang SY, Kang JH. Headache among CADASIL patients with R544C mutation: prevalence, characteristics, and associations. *Cephalalgia*. 2014; 34(1):22-28. doi:10.1177/0333102413497598
21. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414. doi:10.1212/wnl.43.11.2412-a
22. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22(7):602-618. doi: 10.1016/S1474-4422(23)00131-X
23. Zhang R, Chen CH, Tezenas Du Montcel S, et al. The CADA-MRIT: an MRI inventory tool for evaluating cerebral lesions in CADASIL across cohorts. *Neurology*. 2023;101(17):e1665-e1677. doi:10.1212/WNL.0000000000207713
24. O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. *Neurology*. 2001;56(5):628-634. doi:10.1212/wnl.56.5.628
25. Joo L, Shim WH, Suh CH, et al. Diagnostic performance of deep learning-based automatic white matter hyperintensity segmentation for classification of the Fazekas scale and differentiation of subcortical vascular dementia. *PLoS One*. 2022;17(9): e0274562. doi:10.1371/journal.pone.0274562
26. Suh CH, Shim WH, Kim SJ, et al. Development and validation of a deep learning-based automatic brain segmentation and classification algorithm for Alzheimer disease using 3D T1-weighted volumetric images. *AJNR Am J Neuroradiol*. 2020;41(12): 2227-2234. doi:10.3174/ajnr.A6848
27. Arboix A, Cartanyà A, Lowak M, et al. Gender differences and woman-specific trends in acute stroke: results from a hospital-based registry (1986-2009). *Clin Neurol Neurosurg*. 2014;127:19-24. doi:10.1016/j.clineuro.2014.09.024
28. Fandler-Höfler S, Eppinger S, Ambler G, et al. Sex differences in frequency, severity, and distribution of cerebral microbleeds. *JAMA Netw Open*. 2024;7:e2439571. doi: 10.1001/jamanetworkopen.2024.39571
29. Jimenez-Sanchez L, Hamilton OKL, Clancy U, et al. Sex differences in cerebral small vessel disease: a systematic review and meta-analysis. *Front Neurol*. 2021;12:756887. doi:10.3389/fneur.2021.756887
30. Pabidi MR, Kuppusamy M, Didion SP, Sanapureddy P, Reed JT, Sontakke SP. Sex differences in the vascular function and related mechanisms: role of 17 β -estradiol. *Am J Physiol Heart Circ Physiol*. 2018;315(6):H1499-H1518. doi: 10.1152/ajpheart.00194.2018
31. Lohner V, Pehlivan G, Sanroma G, et al. Relation between sex, menopause, and white matter hyperintensities: the Rhineland Study. *Neurology*. 2022;99(9):e935-e943. doi: 10.1212/WNL.00000000000020782
32. van den Heuvel DM, Admiraal-Behloul F, ten Dam VH, et al. Different progression rates for deep white matter hyperintensities in elderly men and women. *Neurology*. 2004;63(9):1699-1701. doi:10.1212/01.wnl.0000143058.40388.44
33. Yoon CW, Rha JH, Park HK, et al. Sex differences in the progression of cerebral microbleeds in patients with concomitant cerebral small vessel disease. *Front Neurol*. 2022;13:1054624. doi:10.3389/fneur.2022.1054624
34. McNeill AM, Zhang C, Stanczyk FZ, Duckles SP, Krause DN. Estrogen increases endothelial nitric oxide synthase via estrogen receptors in rat cerebral blood vessels: effect preserved after concurrent treatment with medroxyprogesterone acetate or progesterone. *Stroke*. 2002;33(6):1685-1691. doi:10.1161/01.str.0000016325.54374.93
35. Cote S, Perron TL, Baillargeon JP, Bocti C, Lepage JF, Whittingstall K. Association of cumulative lifetime exposure to female hormones with cerebral small vessel disease in postmenopausal women in the UK Biobank. *Neurology*. 2023;101(20):e1970-e1978. doi:10.1212/WNL.000000000000207845
36. Abi-Ghanem C, Robison LS, Zuloaga KL. Androgens' effects on cerebrovascular function in health and disease. *Biol Sex Differ*. 2020;11(1):35. doi:10.1186/s13293-020-00309-4
37. Opherk C, Peters N, Holtmannspötter M, Gschwendtner A, Müller-Myhsok B, Dichgans M. Heritability of MRI lesion volume in CADASIL: evidence for genetic modifiers. *Stroke*. 2006;37(11):2684-2689. doi:10.1161/01.STR.0000245084.35575.66
38. Reue K, Wiese CB. Illuminating the mechanisms underlying sex differences in cardiovascular disease. *Circ Res*. 2022;130(12):1747-1762. doi:10.1161/CIRCRESAHA.122.320259
39. Sakkers TR, Mokry M, Civelek M, et al. Sex differences in the genetic and molecular mechanisms of coronary artery disease. *Atherosclerosis*. 2023;384:117279. doi: 10.1016/j.atherosclerosis.2023.117279
40. Choi JC, Song SK, Lee JS, Kang SY, Kang JH. Diversity of stroke presentation in CADASIL: study from patients harboring the predominant NOTCH3 mutation R544C. *J Stroke Cerebrovasc Dis*. 2013;22(2):126-131. doi:10.1016/j.jstrokecerebrovasdis.2011.07.002
41. Yamamoto Y, Liao YC, Lee YC, Ihara M, Choi JC. Update on the epidemiology, pathogenesis, and biomarkers of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *J Clin Neurol*. 2023;19(1):12-27. doi: 10.3988/jcn.2023.19.1.12
42. Chen S, Ni W, Yin XZ, et al. Clinical features and mutation spectrum in Chinese patients with CADASIL: a multicenter retrospective study. *CNS Neurosci Ther*. 2017; 23(9):707-716. doi:10.1111/cns.12719
43. Mykkanen K, Savontaus ML, Juvonen V, et al. Detection of the founder effect in Finnish CADASIL families. *Eur J Hum Genet*. 2004;12:813-819. doi:10.1038/sj.ejhg.5201221
44. Ueda A, Ueda M, Nagatoshi A, et al. Genotypic and phenotypic spectrum of CADASIL in Japan: the experience at a referral center in Kumamoto University from 1997 to 2014. *J Neurol*. 2015;262(8):1828-1836. doi:10.1007/s00415-015-7782-8
45. Hack RJ, Gravestijn G, Cerfontaine MN, et al. Three-tiered EGF α domain risk stratification for individualized NOTCH3-small vessel disease prediction. *Brain*. 2023; 146(7):2913-2927. doi:10.1093/brain/awac486