

Supplementary Table 2. Change in neuroimaging markers

	Baseline MRI	Follow-up MRI	Annual change
PVWM Fazekas score	3 (2–3)	3 (2–3)	-
DWM Fazekas score	3 (2–3)	3 (2–3)	-
EPVS–basal ganglia	3 (2–3)	3 (2–3)	-
EPVS–centrum semiovale	1 (1–2)	1 (1–2)	-
Lacune numbers	5 (2–11)	6 (2–12)	0 (0–1)/0.5±1.3
CMB numbers	8 (2–35)	9 (2–42)	1 (0–4)/2.9±4.1
Lobar CMB numbers	2 (0–12)	3 (0–15)	-
Deep CMB numbers	3 (1–15)	4 (1–20)	-
Infratentorial CMB numbers	1 (0–3)	1 (0–4)	-
WML volume (mL)	39.5±23.8	43.1±25.0	-
WML proportion, % eTIV	2.72±1.59	2.88±1.64	0.23±0.31
Cortical thickness (mm)	2.36±0.13	2.33±0.13	-0.03±0.05
Brain parenchymal fraction, % eTIV	73.00±5.14	72.55±5.27	-0.003±0.02

Values are presented as median (interquartile range) or mean±standard deviation.

MRI, magnetic resonance imaging; PVWM, periventricular white matter; DWM, deep white matter; EPVS, enlarged perivascular space; CMB, cerebral microbleed; WML, white matter lesion; eTIV, estimated total intracranial volume.

Supplementary Table 3. Clinical features and outcomes between *NOTCH3* R544C and non-R544C variant carriers

	R544C (n=81)	Non-R544C (n=10)	P
Age (yr)	64.0±9.7	56.5±13.9	0.03
Male sex	53 (65.4)	6 (60.0)	0.74
History of stroke	50 (61.7)	5 (50.0)	0.51
Ischemic stroke	34 (42.0)	4 (40.0)	0.99
Intracerebral hemorrhage	20 (24.7)	1 (10.0)	0.44
MRI markers			
Lacune numbers	5 (2–10)	5 (2–11)	0.94
CMB numbers	9 (2–40)	3 (0–11)	0.08
WML volume (mL)	39.0±23.4	43.6±27.5	0.47
WML proportion, % eTIV	2.67±1.55	3.08±1.98	0.43
Cortical thickness (mm)	2.36±0.11	2.37±0.25	0.17
Brain parenchymal fraction, % eTIV	72.37±4.56	78.71±6.90	<0.01
Outcomes			
Incident stroke	9 (11.1)	0 (0)	0.59
Incident lacune	25 (30.9)	1 (10.0)	0.27
Increased CMB 2/year	36 (44.4)	1 (10.0)	0.04

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

CMB, cerebral microbleed; eTIV, estimated total intracranial volume; MRI, magnetic resonance imaging; WML, white matter lesion.

Supplementary Table 4. Effects of blood pressure or hypertension on clinical outcome when including patients who do not have follow-up MRI in the analysis

	Incident stroke (updated n=122)		
	Yes (n=9)	No (n=113)	Adjusted HR (95% CI)*
SBP, mean (mm Hg) [†]	122.4±9.1	119.5±10.5	1.39 (0.71, 2.70)
SBP, SD (mm Hg)	6.7±2.3	8.7±2.5	0.87 (0.62, 1.22)
DBP, mean (mm Hg) [†]	77.9±9.2	73.6±7.8	1.96 (0.76, 5.08)
DBP, SD (mm Hg)	5.6±1.6	6.1±1.4	1.18 (0.73, 1.91)
PP, mean (mm Hg) [†]	44.7±5.9	45.9±9.0	0.96 (0.41, 2.26)
PP, SD (mm Hg)	4.8±1.3	7.0±2.1	0.60 (0.32, 1.12)
SBP >130 mm Hg	2 (22.2)	14 (11.5)	2.19 (0.44, 10.88)
DBP >80 mm Hg	5 (55.6)	20 (17.7)	5.59 (1.34, 23.3) [*]

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.

MRI, magnetic resonance imaging; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure; PP, pulse pressure.

Adjusted for age, sex, hypertension, and history of stroke; [†]Effect estimates are expressed as per 10-mm Hg increase in blood pressure; ^{}Statistically significant.