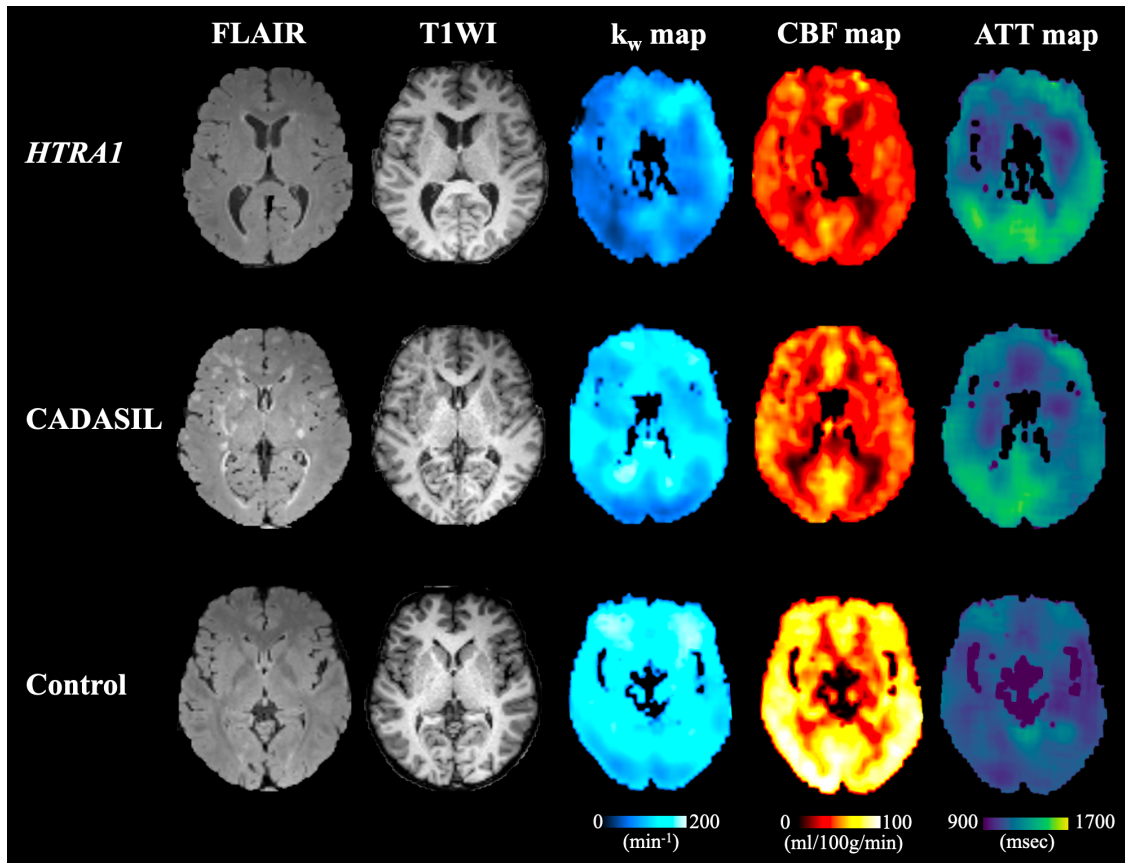


Supplementary Fig.1 Comparison of FLAIR, T1 weighted images, blood-brain barrier water exchange (k_w), cerebral blood flow (CBF) and arterial transit time (ATT) maps of a representative patient with heterozygous HTRA1 mutation related CSVD (27-year-old male) (top row), a patient with CADASIL (29-year-old male) (middle row) and a healthy control (28-year-old female) (bottom row). Decreased k_w , CBF and increased ATT can be observed in the heterozygous HTRA1 mutation related patient and CADASIL patient. In the patient with heterozygous HTRA1 mutation related CSVD: average k_w = 88.3 min⁻¹, average CBF = 35.5 ml/100g/min, average ATT = 1249.7 ms; in the patient with CADASIL: average k_w = 115.2 min⁻¹, average CBF = 40.0 ml/100g/min, average ATT = 1237.6 ms; in the healthy control: average k_w = 143.8 min⁻¹, average CBF = 65.5 ml/100g/min, average ATT = 1161.7ms.



Supplementary Table 1 Details of gene mutation of **CADASIL** group and heterozygous **HTRA1** mutation related

CSVD group

Types of gene mutation	Number
NOTCH3 variant	
c.709G>A, p.Val237Met	1
c.505C>T, p.Arg169Cys	1
c.499C>T, p.Pro167Ser	3
c.421C>T, p.Arg141Cys	3
c.328C>T, p.Arg110Cys	1
c.268C>T, p.Arg90Cys	2
c.226T>C, p.Cys76Arg	1
c.3226C>T, p.Arg337Cys	1
c.1819C>T, p.Arg607Cys	6
c.1645C>T, p.Cys549Ser	1
c.1630C>T, p.Arg544Cys	3
c.1010A>G, p.Tyr337Cys	1
Heterozygous HTRA1 mutation	
c.954G>C, p.Gln318His	7
c.835G>A, p.Val279Met	2

Supplementary Table 2 Cognitive data for HC group, CADASIL group and heterozygous HTRA1 mutation related CSVD group

Table 2A, Compared neuropsychological test scores between CADASIL group, heterozygous HTRA1 mutation related CSVD group and HC group

Neuropsychological test	HC	CADASIL	HTRA1	P value
MMSE	28.00 (1.00)	29.00 (2.00)	28.00 (6.00)	0.914
HAMD	2.50 (3.25)	1.00 (5.50)	5.22 ± 4.92	0.467

Table 2B, Compared neuropsychological test scores between heterozygous HTRA1 mutation related CSVD group and HC group

Neuropsychological test	HTRA1	HC	P value
MoCA subdomains			
Visuospatial/	3.00 ± 1.87	5.00 (1.00)	0.018
Executive Naming	3.00 (0.00)	3.00 (0.75)	0.105
score Attention	5.00 (4.00)	6.00 (1.00)	0.007
score Language score	3.00 (2.00)	2.00 (1.00)	0.492
Abstraction score	2.00 (0.00)	2.00 (1.00)	0.078
Delayed recall score	2.95 ± 1.67	3.00 (2.00)	0.468
Orientation score	6.00 (1.00)	6.00 (0.75)	0.900

Table 2C, Compared neuropsychological test scores between CADASIL group and HC group

Neuropsychological test	CADASIL	HC	P value
Executive function TMT-			
A, second	49.71 ± 21.94	50.00 (42.00)	0.465
TMT-B, second	121.83 ± 50.36	98.26 ± 33.19	0.107
DST (backward)	3.38 ± 2.06	5.40 ± 2.21	0.004
Stroop interference, second	77.00 ± 20.93	59.91 ± 13.01	0.010
Visuospatial ability			
Rey-copy	33.5 (8.25)	35.00 (2.00)	0.066
Rey-memory	18.42 ± 9.16	19.92 ± 7.79	0.593
Language			
Boston naming	26.00 (7.00)	22.68 ± 3.64	0.208
Verbal fluency-animal	15.52 ± 6.36	18.95 ± 6.42	0.095
Memory			
AVLT-immediate recall	6.04 ± 2.14	7.15 ± 1.73	0.043
AVLT-short delayed recall	7.00 ± 2.72	8.00 ± 2.85	0.098
AVLT-long delayed recall	6.41 ± 2.74	8.06 ± 2.86	0.017

Note: Data were presented as mean ± SD or median (interquartile range). Abbreviations: HC: healthy controls; MMSE: Mini-Mental State Examination; HAMD: Hamilton Depression Scale; MoCA: Montreal Cognitive Assessment; TMT: Trail-Making Test; DST: Digit Span Task; AVLT: Auditory Verbal Learning Test.

Supplementary Table 3 Compared CBF (ml/100g/min) between CADASIL group, heterozygous HTRA1 mutation related CSVD group and HC group

Brain regions	HC	CADASIL	HTRA1	P value
Whole brain	47.95 (12.98)	38.09 ± 12.63	32.12 ± 9.00	< 0.001 ^{a,b}
NAWM	42.68 (12.29)	31.11 ± 11.28	23.94 ± 3.90	< 0.001 ^{a,b}
Frontal lobe	44.50 ± 11.08	30.86 ± 11.35	28.33 ± 8.27	< 0.001 ^{a,b}
Parietal lobe	35.47 (16.11)	23.38 (12.78)	23.37 ± 8.12	0.001 ^{a,b}
Temporal lobe	48.88 (11.60)	37.39 ± 13.32	32.36 ± 9.44	< 0.001 ^{a,b}
Caudate nucleus	30.16 ± 8.32	24.67 ± 10.05	19.85 (12.83)	0.024 ^a
Putamen	43.86 (10.12)	38.27 ± 10.97	35.76 ± 7.40	0.033

Note: Data are mean ± SD or median (IQR). Abbreviations: HC: healthy controls; CBF = cerebral blood flow.

Symbols:

- a. for the comparison between the CADASIL and HC (Bonferroni -corrected $p < 0.05$).
- b. for the comparison between the HTRA1 and HC (Bonferroni -corrected $p < 0.05$).
- c. for the comparison between the CADASIL and HTRA1 (Bonferroni -corrected $p < 0.05$).

Supplementary Table 4 Compared ATT (ms) between CADASIL group, heterozygous HTRA1 mutation related CSVD group and HC group

Brain regions	HC	CADASIL	HTRA1	P value
Whole brain	1191.40 (165.55)	1328.76 ± 163.97	1375.02 ± 137.92	0.022
NAWM	1086.89 (169.87)	1174.40 ± 148.91	1257.18 ± 117.41	0.177
Frontal lobe	1028.74 (156.17)	1000.43 ± 162.95	1071.63 ± 163.06	0.602
Parietal lobe	949.24 ± 207.79	1015.88 ± 236.45	1082.65 ± 225.79	0.302
Temporal lobe	982.48 (197.60)	1133.56 ± 183.86	1244.08 ± 128.09	0.003 ^{a,b}
Caudate nucleus	974.60 (133.87)	987.90 ± 145.97	1067.18 ± 109.05	0.271
Putamen	1106.49 (143.79)	1219.92 ± 154.73	1255.60 ± 182.39	0.173

Note: Data are mean ± SD or median (IQR). Abbreviations: HC: healthy controls; ATT = arterial transit time.

Symbols:

- a. for the comparison between the CADASIL and HC (Bonferroni -corrected $p < 0.05$).
- b. for the comparison between the HTRA1 and HC (Bonferroni -corrected $p < 0.05$).
- c. for the comparison between the CADASIL and HTRA1 (Bonferroni -corrected $p < 0.05$).

Supplement Table 5 Multiple linear regression analysis of neuropsychological performance and k_w in CADASIL group

	Brain region	β	P value	95% CI
CADASIL				
AVLT-immediate recall				
	Whole brain	0.334	0.013	0.008 - 0.059
	NAWM	0.345	0.009	0.011 - 0.064
	Temporal lobe	0.284	0.045	0.001 - 0.056
	Putamen	0.366	0.003	0.017 - 0.072
AVLT-long delayed recall				
	Whole brain	0.458	0.001	0.026 - 0.092
	NAWM	0.474	0.001	0.032 - 0.101
	Frontal lobe	0.401	0.004	0.018 - 0.082
	Temporal lobe	0.413	0.007	0.016 - 0.090
	Putamen	0.480	< 0.001	0.040 - 0.110
Heterozygous HTRA1 mutation related CSVD				
Attention score				
	Whole brain	0.844	0.008	0.020 - 0.089
	NAWM	0.814	0.014	0.017 - 0.101
	Frontal lobe	0.813	0.014	0.018 - 0.110
	Parietal lobe	0.822	0.012	0.024 - 0.130
	Temporal lobe	0.821	0.012	0.019 - 0.108

Abbreviations: AVLT: Auditory Verbal Learning Test.

Note: The multivariate linear regression (stepwise) was performed to correct the age, gender, and education level, and the Bonferroni correction was used to correct the number of ROI and cognitive function domains. For CADASIL group, the corrected $p = 0.05 / (5*2) = 0.005$; for HTRA1 group, the corrected $p = 0.05 / (5*1) = 0.01$.