Supplementary table 1. Clinical and genetic data of probands with CSVD related to heterozygous *HTRA1* mutations

Number	Mutations	cDNA changes	Protein domain	Sex	Vascular risk factors	Age of onset (years)	Onset of stroke/TIA (years)	Onset of chronic symptoms (cog, gait, or psychiatic disorder) (years)	Age at examination (years)	Cognitive decline (at examination)	Gait disorder	Psychiatric disorders	Alopecia	Spondylosis	Family history (stroke, dementia, or WMH)	Anterior temporal	External capsule
1[21]	p.R302Ter	c.904C >T	1	M	–	59	59	59	63	2	1	NK	0	0	0	0	1
2[22]	p.R302Ter	c.904C >T	1	M	smoke, alcohol	49	49	55	56	0	1	NK	0	0	1	NK	1
3[23]	p.R166C	c.496C>T	0	M	–	NK	–	–	31	1	0	0	1	0	1	0	0
4[24]	p.R166C	c.496C>T	0	M	smoke	41	41	41	43	9	0	1	0	0	1	1	1
5	p.R166C	c.496C>T	0	F	–	35	35	35	38	1	1	1	1	1	1	1	1
6[29]	p.R302Q	c.905G>A	1	M	Alcohol	40	–	40	57	9	1	NK	1	1	1	NK	NK
7[29]	p.R302Q	c.905G>A	1	M	Alcohol, smoke	44	–	44	61	9	1	NK	1	1	1	0	1
8[25]	p.R302Q	c.905G>A	1	M	–	35	35	NK	41	2	NK	NK	0	0	1	NK	NK
9[26]	p.S284N	NK	1	M	Lipid, impaired glucose tolerance	60	64	60	64	9	1	NK	1	1	0	1	1
10[26]	p.V216M	NK	1	M	HTN, Lipid, smoke	48	48	–	48	9	1	NK	1	1	0	1	1
11[27]	p.Q151Ter	c.451 C>T	2	F	HTN	29	29	59	63	0	1	1	0	1	1	NK	NK
12[28]	p.G120D	c.359G>A	2	F	HTN	52	52	NK	53	1	NK	0	0	0	1	0	1
13[28]	p.I179N	c.536T>A	0	M	HTN, lipid coronary artery disease	48	48	–	50	0	0	0	0	1	1	0	1
14[28]	p.A182PfsTer 33	c.543delT	0	M	HTN, smoke	62	63	62	64	0	1	1	0	1	1	0	1
15[28]	p.I256T	c.767T>C	1	M	HTN	54	–	54	60	2	NK	1	0	1	1	0	1
16[28]	p.G276A	c.827G>C	1	F	Lipid	49	49	NK	56	0	1	1	0	1	1	1	1
17[28]	p.Q289Ter	c.865C>T	1	F	–	55	55	55	64	0	NK	1	1	1	1	1	1
18[28]	p.N324T	c.971A>C	1	M	–	60	60	65	65	1	1	0	0	1	0	1	1
19	p.N324T	c.971A>C	1	F	–	37	37	38	40	1	1	1	0	1	1	1	1
20[20]	p.R166L	c.497 G>T	0	M	Lipid	66	69	66	69	0	1	1	0	1	1	0	1
21[20]	p.A173P	c.517 G>C	0	F	HTN	65	–	65	72	9	1	NK	0	0	1	0	NK
22[29]	p.G283E	c.848G>A	1	M	Alcohol, smoke	49	–	49	49	9	1	NK	0	1	1	NK	NK
23[20]	p.S284R	c.852 C>A	1	F	HTN	NK	–	–	49	0	0	0	0	1	1	0	1
24[20]	p.P285Q	c.854 C>A	1	M	–	50	50	NK	55	0	1	NK	0	0	1	0	NK
25[29]	P.P285L	c.854C>T	1	M	HTN	32	32	32	51	9	1	NK	1	1	0	1	1
26[29]	P.P285L	c.854C>T	1	M	smoke	51	51	53	59	9	1	NK	0	1	0	NK	NK
27[20]	p.F286V	c.856 T>G	1	M	–	49	49	NK	55	9	1	NK	0	0	1	0	1
28[20]	p.D450H	c.1348 G>C	3	M	HTN	68	68	NK	72	9	1	NK	0	0	1	NK	NK
29[20]	p.S284G	c.850 A>G	1	F	–	62	62	–	62	0	0	NK	0	0	1	0	1
30[20]	p.A123S	c.367 G>T	2	M	HTN	NK	–	–	50	0	0	NK	0	0	1	0	0
31[20]	p.R133G	c.397 C>G	2	F	–	NK	–	–	58	0	0	NK	0	0	1	NK	NK
32[20]	p.S121R	c.361 A>C	2	M	–	56	–	56	66	3	1	NK	0	0	1	NK	NK
33[20]	p.Y325_L335 del	c.973–1 G>A	1	F	HTN	66	66	NK	66	NK	NK	NK	0	1	1	0	1
34[29]	p.T319I	c.956C>T	1	M	HTN, Lipid	53	53	53	57	9	1	NK	0	1	NK	NK	NK
35[30]	p.S136G	NK	2	F	–	63	63	63	77	3	1	1	0	0	1	0	NK
36[30]	p.Q151K	c.451C>A	2	M	–	59	–	59	61	2	1	NK	0	0	1	0	1
37[31]	p.Q151K	c.451C>A	2	M	–	59	–	59	60	2	1	NK	0	0	1	NK	1
38[30]	p.V175M	c.523G > A	0	M	HTN, Lipid	59	59	59	77	9	1	NK	0	0	1	0	NK
39	p.V175M	c.523G > A	0	M	HTN, DM	49	49	53	54	1	1	1	1	1	1	1	1
40[30]	p.G206E	NK	1	M	HTN	55	–	55	65	9	1	1	0	0	1	0	NK
41[30]	p.G295R	NK	1	M	–	65	–	65	73	9	1	1	0	0	1	0	NK
42[32]	p.V176A	c.527T>C	0	M	HTN	64	64	64	71	2	1	1	1	NK	1	NK	1
43[32]	p.R197Ter	c.589C>T	0	M	HTN	77	77	77	78	3	1	NK	NK	NK	1	NK	1
44[33]	p.G283R	c.847G>A	1	M	–	32	–	32	39	9	1	NK	0	1	0	0	1

Protein domain: 0=outside the protease domain; 1=Trypsin-like serine protease domain; 2=Kazal-type serine protease domain; 3=PDZ domain. Cognitive decline: 0=normal (MMSE≥27, or MoCA≥27, or described as “normal” in the article); 1=mild (MMSE 21–26, or MoCA 18–26); 2=moderate (MMSE 10–20, or MoCA 10–17); 3=severe (MMSE≤9, or MoCA<10, or described as “severe” or “dementia” in article); 9= have cognitive impairment but without detailed information. NK: not known; 0: no;1: yes; Lipid: hyperlipidemia; HTN: hypertension; CAD: coronary artery disease; TIA: transient ischemic attack.

Supplementary table 2. Clinical and genetic data of CARASIL probands

Numbers	Mutations	cDNA changes	Protein domain	Sex	Vascular risk factors	Age of onset (years)	Onset of stroke/TIA (years)	Onset of chronic symptoms (cog, gait, or psychiatic disorder) (years)	Age at examination (years)	Cognitive decline (at examination)	Gait disorder	Psychiatric disorders	Alopecia	Spondylosis	Family history (stroke, dementia, or WMH)	Anterior temporal	External capsule
1[2]	p.A252T	c.754G>A	1	F	–	38	38	38	48	3	1	NK	0	1	1	NK	NK
2[2]	p.V297M	c.889G>A	1	F	–	31	–	31	50	3	1	NK	1	1	1	NK	NK
3[2]	p.V297M	c.889G>A	1	M	–	29	–	29	33	3	1	NK	1	1	1	NK	NK
4[2]	p.R302Ter	c.904C>T	1	M	–	26	31	26	28	3	1	NK	1	1	1	NK	NK
5[2]	p.R302Ter	c.904C>T	1	F	–	29	–	29	46	3	1	NK	1	1	NK	NK	NK
6[11]	p.R370Ter	c.1108C>T	3	F	–	27	–	27	29	0	1	NK	1	1	0	1	NK
7[2]	p.R370Ter	c.1108C>T	3	F	–	35	–	35	44	3	1	NK	1	1	0	NK	NK
8[7]	p.R274Q	c.821G>A	1	F	NK	Early 20's	–	Early 20's	44	9	1	NK	0	1	1	NK	NK
9[6]	p.G295R	c.883G>A	1	M	Alcohol, smoke	Before 34	–	Before 34	43	9	1	1	1	1	1	1	1
10[8]	p.L364P	c.1091T>C	1	F	–	27	27	27	27	9	1	NK	1	1	1	NK	NK
11[9]	p.P285L	c.854C>T	1	F	–	23	23	23	26	3	1	1	1	1	1	NK	NK
12[12]	p.R166C	c.496C>T	0	M	–	31	31	NK	45	3	1	NK	1	1	1	1	0
13[13]	p.A173T	c.517G>A	0	F	–	35	35	37	37	9	1	1	1	1	1	NK	NK
14[16]	p.G206R	c.616G>A	1	M	–	24	24	24	25	9	1	NK	1	1	0	1	0
15[18]	p.S328Ter	c.983C>A	1	M	NK	26	26	30	35	9	1	1	1	1	0	1	1
16[10]	p.A321T/p.Q42fs	c.961G>A/c.126delG	1/4	F	–	24	24	–	29	0	1	NK	0	1	0	1	1
17[17]	p. D320N/p.G341J	c.958G > A/c.1021G > A	1/1	F	–	40	40	–	40	0	0	NK	1	1	0	1	1
18[14]	p.G56AfsTer160	c.161_162insAG	4	M	–	28	28	–	28	NK	NK	NK	1	1	1	1	1
19[15]	p.E247Rfs	c.739delG	1	M	NK	25	–	25	26	9	1	1	1	1	0	1	1

20[15]	p.E277Vfs	c.830_831delAG	1	M	NK	22	–	22	24	NK	1	1	1	NK	1	1	1
21[15]	p.K168Ter	c.502A＞T	0	F	NK	32	32	33	33	9	1	NK	1	1	0	1	1
22[19]	P.S270LfsTer 69	c.805_806insG	1	F	NK	early 30's	NK	NK	32	1	1	1	1	1	1	NK	NK

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