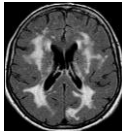
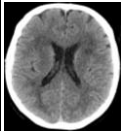
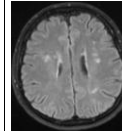
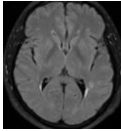
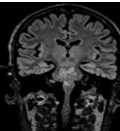
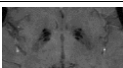
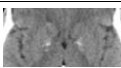
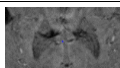
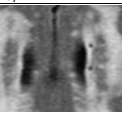
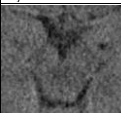
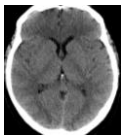
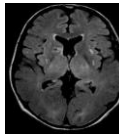
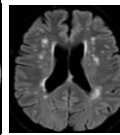
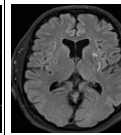
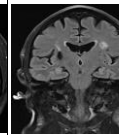
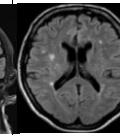
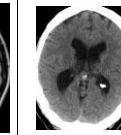
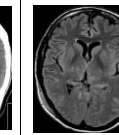
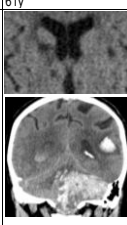
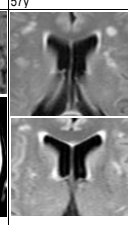
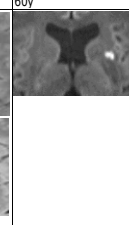
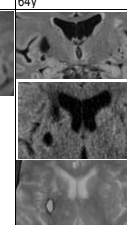
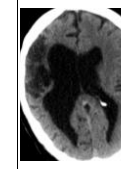


Supplemental Table e1: Detailed clinical information

| | II.1 | II.2 | II.3 | III.3 | III.4 | III.5 | III.6 | III.7 | III.11 |
|---|--|--|---|--|---|--|---|---|---|
| Age at first symptom | 69y | 59y | around 60y | 52y | - | - | 39y | 36y | around 60y |
| First symptom | Stroke | Stroke | Orthostatic hypotension, and urine incontinence | Stroke | Asymptomatic | Asymptomatic | Symptomatic orthostatic hypotension | Sleeping problems, panic attacks, diagnosed with ADHD | Balance instability |
| Age at first stroke episode | 69y | 59y | - | 52y | - | - | | | - |
| Clinical symptoms at first stroke episode | Left facial, arm and leg palsy | Left arm and leg palsy | No clinically manifest stroke | Hemisensory loss right face, arm, leg | No clinically manifest stroke | No clinically manifest stroke | No clinically manifest stroke | No clinically manifest stroke | No clinically manifest stroke |
| Age at MRI/CT | CT 71y | CT 59y | 76y | CT 59y | 57y | - | 53y | CT 44y | 66y |
| Images illustrating white matter hyperintensities | Images not retrieved, but radiology reports available. | Images not retrieved, but radiology reports available. |  |  |  | |  | CT normal at age 44 |  |
| White matter changes on radiology | Yes | Yes | Yes | Yes | Yes | N/D | Yes | No | Yes |
| Age at MRI/CT: Basal ganglia calcifications | | | | | 57y | | 54y | | 57y |
| | | | | |  | |  | |  |
| Age at MRI/CT: Lacunar infarcts/ICH | | | 76y | 47y | | | | | |
| | | |  |  | | | | | |
| Lacunar infarcts/ICH | Yes (acc to radiology reports) | Yes (acc to radiology reports) | Yes (lacunes) | Yes. Also lacunes at autopsy (died 53y). | No | | No | No | No |
| Movement disorders | ND | Gait disturbance, ataxia cc to medical records. | Cerebellar tremor/Dyscoordination, irregular horizontal eye movements on smooth pursuit | Tremor considered related to abstinence | Mild cerebellar signs (left>right hand dysmetria and dysidiadochokinesis, instability with tandem gait). No tremor. | ND | Mild positional hand tremor. | Bilateral postural tremor in arms and legs | Gait disturbance |
| Cognitive dysfunction /depression | ND | Severe depression | Cognitive dysfunction | Severe depression, ECT treated. Short memory problems, difficulty concentrating | Cognitive dysfunction | ND | Depression, sleeping problems | Anxiety, sleep problems | Cognitive dysfunction |
| MoCA/MMSE/ progression | ND | ND | MMSE 23/30 | ND | MoCA 22/30 | ND | MoCA 21/30 | MoCA 26/30 | MoCA 24/30 (65y); MoCA 22/30 (66y) |
| Clinical status | Undetermined | Undetermined | Affected | Affected | Affected | Undetermined | Affected | Undetermined | Affected |
| MAP3K6 c.322G>A genotype | Obligate carrier | Obligate carrier | Obligate carrier | Not tested | MUT/wt | wt/wt | MUT/wt | MUT/wt | MUT/wt |
| Vascular risk factors | Mix2, Ap, Obe, episodes of VT, claudicatio | Smo, Ob, AF, dilated CMY, Dm, DVT | Smo | Smo, alcohol. Mild HT. MI at autopsy. | None | Smo, Ap, Obe, sleep apnea | AF | AF | none |
| Migraine | No | No | No | ND | No | No | No | No | migraine |
| ANS dysfunction | Not known | Syncope, OH | Syncope, OH | ND | Syncope, OH | - | OH (diagnosed at age 39) | OH episodes (47y-49y) | ND |
| Other clinical information | Rectal cancer. Gastric ulcer. | Peptic ulcer. | Kidney malformation | Gastric and duodenal ulcers since 25y. Anthracosis at autopsy. | Leiomyoma | Hiatus hernia, colonic diverticulitis, back pain. | - | Disc herniation, operated at age 34yr. | Back pain |
| Large vessel examinations | ND | ND. At stroke episode normal findings in CSF. | ND | Cran CTA: normal. | ND | Cor angio (54y): moderate atheromatosis. CTA aorta (56y): normal. Cran CTA not performed. | Cor angio (50y): no stenoses, CTA aorta (50y) normal. Cran CTA (54y) normal. | ND | ND |
| Cardiological examinations | ECGs: sinus rhythm, 2nd degree atrioventricular block, acute MI. | TTE: moderate LVH, hypokinesia, secondary mitral valve failure. ECG at stroke-episode: normal, sinus rhythm. | ECG: sinus rhythm, normal. | ECG: sinus rhythm. Normal/max. normal BP. No TTE/TEE. | ECG x6 (56y to 60y): normal. No TTE. | TTE (at 54y): normal, except diastolic relaxation dysfunction. ECG: normal (x11, between 51-58y) | TTEx7 (50y-57y): always normal function; ECG: AF since 50y | TTE at 45y normal. ECG 47y: paroxysmal AF | ECG: sinus rhythm, normal. |
| Post mortem examination | | | | Died at 53y from sudden cardiac arrest. Severe coronary arteriosclerosis and fresh thrombus in right coronary vessel. LVH. Lacunar infarcts in brain, at macroscopic examination. No tissue available. | | | | | |

Supplemental Table e1(ctd.)

| | III.16 | III.17 | III.18 | III.19 | III.20 | III.22 | III.23 | III.24 |
|---|--|--|--|--|--|--|--|---|
| Age at first symptom | - | 48y | 40y | 52y | 58y | 47y | 53 y | - |
| First symptom | Asymptomatic | Hand tremor | Hand tremor | Subjective short-term memory loss, hand tremor | Short-term memory loss; inability to use telephone and computer | Severe depression | Stroke | (Acute traumatic SHD at age 53y) |
| Age at first stroke episode | - | 62y | - | - | 63y | - | 53y | 53y |
| Clinical symptoms at first stroke episode | No clinically manifest stroke | Expressive aphasia. Lethal cerebellar hemorrhage. | No clinically manifest stroke | No clinically manifest stroke | Vertigo, hemisensory loss right arm and leg; motor weakness right arm and leg. | No clinically manifest stroke | Left arm and leg palsy and hemisensory loss, dysarthria, visual hemiplegia. | Posttraumatic SDH, hemiplegia, seizure. |
| Age at MRI/CT | CT at 49y (headache episode) | 56y | 57y | 61y | 64y | 58y | CT 53y | 60y |
| Images illustrating white matter hyperintensities |  |  |  |  |  |  |  |  |
| White matter changes on radiology | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Age at MRT/CT: Basal ganglia calcifications | | | | | | | | |
| Age at MRT/CT | | 61y | 57y | 60y | 64y | | | |
| Lacunar infarcts/ICH | |  |  |  |  | | No lacunes. Territorial infarct due to LAA.  | |
| Lacunar infarcts/ICH | No | Yes (lacunes and ICH) | Yes (lacunes) | Yes (lacunes) | Yes (lacunes and ICH) | No | No, LAA | No |
| Movement disorders | ND | Cerebellar tremor. Bilateral dystaxia, atactic gait. Hypokinesia of hand movements. | Cerebellar tremor, saccadic horizontal eye movements | Cerebellar tremor, mild dystaxia and balance impairment. Mild rigidity. | Cerebellar tremor, mild dystaxia and balance impairment. Hypo/bradykinesia of hand movements. | Tremor, dyscoordination, hypokinesia | ND | No cerebellar signs. Left femispasticity. |
| Cognitive dysfunction /depression | Normal | Cognitive dysfunction, severe depression | Cognitive dysfunction | Subjective cognitive dysfunction | Subjective cognitive dysfunction | Depression | Normal | Non-progressive cognitive dysfunction. Depression. |
| MoCA/MMSE/ progression | - | No | No | MoCA 26/30, subjective decline | MoCA 26/30 | MoCA28/30 | No | Deficit after ICH. No worsening between 53y-58y; MoCA 27/30 |
| Clinical status | Unaffected | Affected | Affected | Affected | Affected | Affected | Unaffected | Unaffected |
| MAP3K6 c.322G>A genotype | Not tested | MUT/wt | MUT/wt | MUT/wt | MUT/wt | MUT/wt | wt/wt | wt/wt |
| Vascular risk factors | HT, LVH, cardiac failure, asystolia episode | Smo, AF | alcohol overconsumption | Ap, previous Smo | HT, AF | HT, previous Smo | Previous Smo, Obe, hyperch, DVT | Smo |
| Migraine | ND | No | No | No | migraine | migraine | No | migraine |
| ANS dysfunction | No | Syncope, OH | ND | ND | Syncope, OH episodes | OH | No | No |
| Other clinical information | COLD, after silitium inhalation, lung-transplant.Back pain. | Peptic ulcer, short stature (160cm) | Short stature; choroidal nevus. | Epigastralgia, prostate cancer. | Gastrocele. Kidney operated (cause ND). Unilateral congenital sensorineural hearing loss. Short stature. | Acute myeloid leukemia (ay 60y). Psoriasis. | Spastic hemiparesis since birth | Situs inversus, cholelithiasis. |
| Large vessel examinations? | ND | Cran CTA (62y): atherosclerotic deposits, occlusion left a. vertebralis (at ICH). No vascular malformations. | ND | Cor CTA: normal. Carotid duplex (61y): normal. CTA aorta: known left iliaca communis occlusion. | Carotid duplex: normal. | ND | Cran CTA: occlusion right ICA | Conventional angiography of supraortic trunks and intracerebral vessels: normal, no AV-fistula or MAV |
| Cardiological examinations | ECG: sinus tachycardia on some registrations. Intermittent cardiac failure. TTE: LVH | TTE (at 62y): moderate LVH, EF 50%. ECG: normal | ECG (at 58y): normal | MRI heart (at 65y): anteroseptal fibrous string. ECG: normal. TTE (most recent at 65y): normal except mild ventricular hypertrophy | ECG: AF | ECGx12 (37y to 61y): normal. TTE (60y): normal except mild LVH. | ECG: normal. TTE: not done | ECG registration: normal. No TTE. |
| Post mortem examination | Yes, but brain was not examined. No tissue available. | Yes. Reported in main text. Only brain was examined due to personal / family wishes. | | | | | | |