SUPPLEMENTARY Materials

## Literature search

#1.

(“Collagen Type IV"[Mesh] AND “alpha?1”[All Fields]) OR (“Collagen Type IV"[Mesh] AND “alpha?2”[All Fields]) OR “Collagen Type IV alpha 1”[All Fields] OR “Collagen Type IV alpha 2”[All Fields] OR “COL4A1 protein, human”[Supplementary Concept] OR “COL4A2 protein, human”[Supplementary Concept] OR COL4A1[All Fields] OR COL4A2[All Fields]

#2.

Stroke[Mesh] OR Stroke[All Fields] OR “Cerebral Small Vessel Diseases”[Mesh] OR “Cerebral Small Vessel Diseases”[All Fields] OR (Cerebral[All Fields] AND Small[All Fields] AND Vessel[All Fields] AND Diseases[All Fields]) OR CSVD[All Fields] OR SVD[All Fields] OR Hemorrhage[Mesh] OR "Hemorrhagic"[All Fields] OR Leukoencephalopathies[Mesh] OR Leukoencephalopathies [All Fields] OR Leukoencephalopathy[All Fields] OR “cerebral aneurysm"[All Fields] OR "intracranial aneurysm"[All Fields] OR (cerebral[All Fields] AND aneurysm[All Fields]) OR (intracranial[All Fields] AND aneurysm[All Fields]) OR "intracerebral hemorrhage"[All Fields] OR "intracerebral haemorrhage"[All Fields] OR (intracerebral [All Fields] AND hemorrhage [All Fields]) OR (intracerebral [All Fields] AND haemorrhage [All Fields]) OR "intracranial hemorrhage"[All Fields] OR "intracranial haemorrhage"[All Fields] OR (intracranial [All Fields] AND hemorrhage [All Fields]) OR (intracranial [All Fields] AND haemorrhage [All Fields]) OR "cerebral hemorrhage"[All Fields] OR "cerebral haemorrhage"[All Fields] OR Microbleeds[All Fields] OR (cerebral [All Fields] AND hemorrhage [All Fields]) OR (cerebral [All Fields] AND haemorrhage [All Fields]) OR Dementia[Mesh] OR Dementia[All Fields] OR "Dementia, Vascular"[Mesh] OR "Vascular Dementia"[All Fields] OR (Vascular[All Fields] AND Dementia[All Fields]) OR "Dementia, Multi-Infarct"[Mesh] OR "Cognitive Dysfunction"[Mesh] OR "Cognitive Dysfunction"[All Fields] OR "Cognitive Impairment"[All Fields] OR (Cognitive[All Fields] AND Impairment[All Fields])

#3.

“autosomal dominant”[All Fields] OR “autosomal recessive”[All Fields] OR familial[All Fields] OR hereditary[All Fields] OR Hematuria[Mesh] OR Hematuria[All Fields] OR “artery tortuosity”[All Fields] OR “arterial tortuosity”[All Fields] OR Porencephaly[Mesh] OR Porencephaly[All Fields]

#4.

“Angiopathy, Hereditary, With Nephropathy, Aneurysms, And Muscle Cramps”[Supplementary Concept] OR HANAC[All Fields] OR (Angiopathy[All Fields] AND Hereditary[All Fields] AND Nephropathy[All Fields] AND Aneurysms[All Fields] AND “Muscle Cramps”[All Fields]) OR PADMAL [All Fields] OR (pontine[All Fields] AND autosomal[All Fields] AND dominant[All Fields] AND microangiopathy[All Fields] AND leukoencephalopathy[All Fields]) OR (“multi-infarct”[All Fields] AND dementia [All Fields] AND Swedish [All Fields]) OR hMID[All Fields] OR HEMID[All Fields]

#1 AND (#2 OR #3) OR #4

## Supplementary Table 1. The results of ACMG classification of excluded mutations

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mutations | rsID | ClinVar | PVS | PS | PM | PP | BS | BP | ACMG criteria |
| *COL4A2* |  |  |  |  |  |  |  |  |  |
| c.3368A>G, p.Glu1123Gly | rs117412802 | Benign/Likely Benign | - | - | 1, 2 | 3 | 4 | 4, 6 | Likely benign |
| c.3448C>A, p.Gln1150Lys | NA | Benign/Likely Benign | - | - | 1, 2 | 3, 4 | - | 4, 6 | Likely benign |
| c.5068G>A, p.Ala1690Thr | rs201105747 | Benign/Likely Benign | - | - | 2 | 3 | - | 4, 6 | Likely benign |

NA indicates not available.

## Supplementary Table 2. Mutations included in this study

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mutations | Mutation Type | Domain | Triplet | Exon,  Intron | Exac3.1  frequency | rsID | ACMG Criteria | Aneurysm | Ref |
| Duplication/CNV | - | - | - | - | - | NA | Uncertain significance | Negative | [1] |
| Duplication/CNV | - | - | - | - | - | NA | Uncertain significance | Negative | [2] |
| Duplication/CNV | - | - | - | - | - | NA | Uncertain significance | Negative | [3] |
| *COL4A1* | | | | | | | | | |
| c.1A>T | Start Codon | Signal | - | 1 | - | NA | Pathogenic | Positive | [4] |
| c.236G>T, p.Gly79Val | Missense | 7S | M-X-Y | 4 | - | NA | Uncertain significance | Negative | [5] |
| c.347C>T, p.Pro116Leu | Missense | 7S | G-M-Y | 6 | 0.00001972 | rs538816765 | Uncertain significance | Positive | [6,7] |
| c.553-2A>G | Splice Site | Triple | - | Intron 9 | - | NA | Pathogenic | Negative | [8] |
| c.1120+2\_1120+8del | Splice Site | Triple | - | Intron 20 | - | NA | Pathogenic | Negative | [9] |
| c.1249G>C, p.Gly417Arg | Missense | Triple | M-X-Y | 21 | - | NA | Pathogenic | Positive | [10] |
| c.1493G>T, p.Gly498Val | Missense | Triple | M-X-Y | 24 | - | NA | Pathogenic | Positive | [11,12] |
| c.1502G>A, p.Gly501Asp | Missense | Triple | M-X-Y | 24 | - | NA | Pathogenic | Positive | [13] |
| c.1528G>A, p.Gly510Arg | Missense | Triple | M-X-Y | 24 | - | NA | Pathogenic | Positive | [14-16] |
| c.1537-2delA | Splice Site | Triple | - | Intron 24 | - | NA | Pathogenic | Negative | [17] |
| p.Arg538Trp | Missense | Triple | Other | 25 | - | NA | Uncertain significance | Positive | [18] |
| c.1555G>A, p.Gly519Arg | Missense | Triple | M-X-Y | 25 | - | NA | Pathogenic | Positive | [11,12] |
| c.1573GG>TT, p.Gly525Leu | Missense | Triple | M-X-Y | 25 | - | NA | Pathogenic | Positive | [16] |
| c.1583G>A, p.Gly528Glu | Missense | Triple | M-X-Y | 25 | - | NA | Pathogenic | Positive | [11,12] |
| c.1937G>C, p.Gly646Ala | Missense | Triple | M-X-Y | 27 | 0.000006573 | rs532972509 | Pathogenic | Negative | [19] |
| c.1942C>G, p.Pro648Ala | Missense | Triple | G-X-M | 27 | 0.000006569 | rs1413099763 | Likely pathogenic | Positive | [20] |
| c.1961C>A, p.Prp654Gln | Missense | Triple | G-X-M | 27 | 0.00001314 | rs758315813 | Likely pathogenic | Positive | [21] |
| c.2063G>A, p.Gly688Asp | Missense | Triple | M-X-Y | 28 | - | NA | Likely pathogenic | Negative | [22] |
| c.2086G>A, p.Gly696Ser | Missense | Triple | M-X-Y | 28 | - | NA | Pathogenic | Negative | [23] |
| c.2159G>A, p.Gly720Asp | Missense | Triple | M-X-Y | 29 | - | NA | Pathogenic | Positive | [24,25] |
| c.2263G>A, p.Gly755Arg | Missense | Triple | M-X-Y | 30 | - | NA | Pathogenic | Positive | [26,27] |
| c.2317G>A, p.Gly773Arg | Missense | Triple | M-X-Y | 30 | - | NA | Pathogenic | Negative | [28] |
| c.2327G>T, p.Gly776Val | Missense | Triple | M-X-Y | 30 | - | NA | Pathogenic | Negative | [29] |
| c.2413G>A, p.Gly805Arg | Missense | Triple | M-X-Y | 31 | - | NA | Pathogenic | Negative | [30] |
| c.2494G>A, p.Gly832Arg | Missense | Triple | M-X-Y | 32 | - | NA | Pathogenic | Negative | [31] |
| c.2504G>A, p.Gly835Glu | Missense | Triple | M-X-Y | 32 | - | NA | Pathogenic | Positive | [32] |
| c.2662G>C, p.Gly888Arg | Missense | Triple | M-X-Y | 33 | - | NA | Pathogenic | Positive | [10] |
| c.2969G>T, p.Gly990Val | Missense | Triple | M-X-Y | 36 | - | NA | Likely pathogenic | Negative | [33] |
| c.3715G>A, p.Gly1239Arg | Missense | Triple | M-X-Y | 42 | - | NA | Likely pathogenic | Positive | [34] |
| c.3734G>A, p.Gly1245Asp | Missense | Triple | M-X-Y | 42 | - | NA | Pathogenic | Positive | Ours |
| c.3797G>T, p.Gly1266Val | Missense | Triple | M-X-Y | 43 | - | NA | Likely pathogenic | Negative | [35] |
| c.3976G>A, p.Gly1326Arg | Missense | Triple | M-X-Y | 45 | - | NA | Pathogenic | Negative | [36] |
| c.4031G>C, p.Gly1344Ala | Missense | Triple | M-X-Y | 46 | - | NA | Likely pathogenic | Negative | [37] |
| c.4150+1G>T | Splice Site | Triple | - | Intron 46 | - | NA | Pathogenic | Negative | [38] |
| c.4380T>G, p.Cys1460Trp | Missense | NC1 | Other | 48 | - | NA | Uncertain significance | Negative | [39] |
| c.4611\_4612insG, p.Thr1537fs | Frameshift | NC1 | Other | 49 | - | NA | Pathogenic | Negative | [40] |
| c.\*32G>A | 3'UTR | - | Other | 3'UTR | - | NA | Likely pathogenic | Negative | [41] |
| c.\*32G>T | 3'UTR | - | Other | 3'UTR | - | NA | Likely pathogenic | Negative | [42] |
| c.\*34G>T | 3'UTR | - | Other | 3'UTR | - | NA | Uncertain significance | Negative | [43] |
| c.\*35C>A | 3'UTR | - | Other | 3'UTR | - | NA | Likely pathogenic | Negative | [44] |
| *COL4A2* | | | | | | | | | |
| c.1837G>A, p.Gly613Ser | Missense | Triple | M-X-Y | 24 | - | NA | Pathogenic | Negative | [45] |
| c.2105G>A, p.Gly702Asp | Missense | Triple | M-X-Y | 28 | - | NA | Pathogenic | Positive | [46] |
| c.2572A>G, p.Ile858Val | Missense | Triple | G-M-Y | 29 | - | NA | Uncertain significance | Negative | [47] |
| c.2821G>A, p.Gly941Arg | Missense | Triple | M-X-Y | 32 | - | NA | Pathogenic | Positive | [48] |
| c.2972G>A, p.Gly991Glu | Missense | Triple | M-X-Y | 32 | - | NA | Pathogenic | Positive | [49] |
| c.3110G>A, p.Gly1037Glu | Missense | Triple | M-X-Y | 33 | - | NA | Pathogenic | Negative | [50] |
| c.3206delC | Frameshift | Triple | Other | 34 | - | NA | Pathogenic | Negative | [51] |
| c.3455G>A, p.Gly1152Asp | Missense | Triple | M-X-Y | 37 | - | NA | Pathogenic | Negative | [50] |
| c.4165G>A, p.Gly1389Arg | Missense | Triple | M-X-Y | 44 | 0.000006574 | NA | Pathogenic | Positive | [51] |
| p.Ala1534Ser | Missense | NC1 | Other | 46 | 0.00001314 | rs760399386 | Uncertain significance | Negative | [52] |

CNV, copy number variant; UTR, untranslated region; NC1, non-collagenous domain; NA, not available. G-M-Y indicates that the mutation is located at the amino acid position after the glycine residue in the glycine triplet sequence. G-X-M indicates that the mutation is located at amino acid position two after the glycine residue in the glycine triplet sequence. M-X-Y indicates that the mutation is located at the glycine position in the glycine triplet sequence.

## Supplementary Table 3. The results of in silico analysis and ACMG classification of included mutations in this study

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mutations | ClinVar | delta score of SpliceAI | | | | MaxEntScan,  %Variance | CADD,  PHRED | PolyPhen2 | SIFT | Provean | ACMG | | | | Ref |
| Acceptor Loss | Donor Loss | Acceptor Gain | Donor Gain | PVS | PS | PM | PP |
| Duplication/CNV | NA | - | - | - | - | - | - | NA | NA | NA | - | - | 2 | 4 | [1] |
| Duplication/CNV | NA | - | - | - | - | - | - | NA | NA | NA | - | - | 2, 6 | 4 | [2] |
| Duplication/CNV | NA | - | - | - | - | - | - | NA | NA | NA | - | - | 2 | 4 | [3] |
| *COL4A1* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| c.1A>T | Pathogenic | - | - | - | - | - | 23.2 | NA | NA | NA | 1 | - | 2 | 5 | [4] |
| c.236G>T, p.Gly79Val | NA | 0 | 0 | 0 | 0 | 4.8 | 33.0 | Probably | Deleterious | Deleterious | - | - | 2 | 3, 4 | [5] |
| c.347C>T, p.Pro116Leu | Uncertain Significance | - | - | - | - | - | 24.1 | Probably | Tolerated | Deleterious | - | - | 2 | 3 | [6,7] |
| c.553-2A>G | NA | 1 | 0 | 0.29 | 0 | 79.6 | 32.0 | NA | NA | NA | 1 | 2 | 1, 2 | 3, 4 | [8] |
| c.1120+2\_1120+8del | NA | 0.13 | 0.99 | 0 | 0.01 | 176.9 | 23.5 | NA | NA | NA | 1 | - | 1, 2 | 1, 3, 4 | [9] |
| c.1249G>C, p.Gly417Arg | NA | - | - | - | - | - | 21.6 | benign | Tolerated | Deleterious | - | 3 | 1, 2 | 3, 4 | [10] |
| c.1493G>T, p.Gly498Val | Pathogenic | - | - | - | - | - | 25.6 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [11,12] |
| c.1502G>A, p.Gly501Asp | Pathogenic/Likely Pathogenic | - | - | - | - | - | 25.8 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [13] |
| c.1528G>A, p.Gly510Arg | Pathogenic/Likely Pathogenic | - | - | - | - | - | 24.2 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 1, 3, 4, 5 | [14-16] |
| c.1537-2delA | NA | 0.98 | 0 | 0.14 | 0.02 | 163.9 | 29.5 | NA | NA | NA | 1 | 2 | 1, 2 | 3, 4 | [17] |
| p.Arg538Trp | Uncertain Significance | - | - | - | - | - | 23.9 | Probably | Tolerated | Deleterious | - | - | 1, 2 | 3 | [18] |
| c.1555G>A, p.Gly519Arg | Pathogenic | - | - | - | - | - | 26.6 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [11,12] |
| c.1573GG>TT, p.Gly525Leu | Pathogenic | - | - | - | - | - | 26 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [16] |
| c.1583G>A, p.Gly528Glu | Pathogenic | - | - | - | - | - | 27.2 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [11,12] |
| c.1937G>C, p.Gly646Ala | NA | - | - | - | - | - | 22.7 | Probably | Tolerated | Deleterious | - | 3 | 1, 2 | 3, 4 | [19] |
| c.1942C>G, p.Pro648Ala | NA | - | - | - | - | - | 22.6 | Probably | Tolerated | Deleterious | - | - | 1, 2 | 3, 4 | [20] |
| c.1961C>A, p.Prp654Gln | NA | - | - | - | - | - | 19.7 | Possibly | Deleterious | Deleterious | - | - | 1, 2 | 3, 4 | [21] |
| c.2063G>A, p.Gly688Asp | NA | - | - | - | - | - | 23.7 | Probably | Tolerated | Neutral | - | 3 | 1, 2 | 3 | [22] |
| c.2086G>A, p.Gly696Ser | Pathogenic | - | - | - | - | - | 27 | Probably | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 4, 5 | [23] |
| c.2159G>A, p.Gly720Asp | Pathogenic/Likely Pathogenic | - | - | - | - | - | 25.5 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [24,25] |
| c.2263G>A, p.Gly755Arg | Pathogenic | - | - | - | - | - | 24.3 | Probably | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 4, 5 | [26,27] |
| c.2317G>A, p.Gly773Arg | Pathogenic | - | - | - | - | - | 24.4 | Probably | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 4, 5 | [28] |
| c.2327G>T, p.Gly776Val | Likely Pathogenic | - | - | - | - | - | 25.8 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [29] |
| c.2413G>A, p.Gly805Arg | Likely Pathogenic | - | - | - | - | - | 25.5 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [30] |
| c.2494G>A, p.Gly832Arg | Pathogenic/Likely Pathogenic | - | - | - | - | - | 27.5 | Possibly | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 4, 5 | [31] |
| c.2504G>A, p.Gly835Glu | NA | - | - | - | - | - | 26.5 | benign | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 4 | [32] |
| c.2662G>C, p.Gly888Arg | Pathogenic/Likely Pathogenic | - | - | - | - | - | 25.9 | Possibly | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 5 | [10] |
| c.2969G>T, p.Gly990Val | Likely Pathogenic | 0.06 | 0 | 0.01 | 0 | 33.0 | 33 | Probably | Deleterious | Deleterious | - | - | 1, 2, 5 | 3, 4, 5 | [33] |
| c.3715G>A, p.Gly1239Arg | Pathogenic | - | - | - | - | - | 26.4 | Probably | Deleterious | Deleterious | - | - | 1, 2 | 3, 4, 5 | [34] |
| c.3734G>A, p.Gly1245Asp | NA | - | - | - | - | - | 26.3 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4 | Ours |
| c.3797G>T, p.Gly1266Val | NA | - | - | - | - | - | 24.1 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3 | [35] |
| c.3976G>A, p.Gly1326Arg | Pathogenic | - | - | - | - | - | 26.9 | Probably | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 5 | [36] |
| c.4031G>C, p.Gly1344Ala | NA | - | - | - | - | - | 24.9 | Possibly | Deleterious | Deleterious | - | 3 | 1, 2 | 3 | [37] |
| c.4150+1G>T | NA | 0 | 0.99 | 0 | 0.05 | 97.9 | 33 | NA | NA | NA | 1 | 2 | 1, 2 | 3, 4 | [38] |
| c.4380T>G, p.Cys1460Trp | NA | - | - | - | - | - | 25.7 | Probably | Deleterious | Deleterious | - | - | 2 | 3 | [39] |
| c.4611\_4612insG, p.Thr1537fs | NA | - | - | - | - | - | 33 | NA | NA | NA | 1 | - | 2 | 4 | [40] |
| c.\*32G>A | Likely Pathogenic | - | - | - | - | - | 19.2 | NA | NA | NA | - | 3 | 2 | 4, 5 | [41] |
| c.\*32G>T | Pathogenic | - | - | - | - | - | 18.7 | NA | NA | NA | - | 3 | 2 | 4, 5 | [42] |
| c.\*34G>T | NA | - | - | - | - | - | 18.9 | NA | NA | NA | - | - | 2 | 4, 5 | [43] |
| c.\*35C>A | Pathogenic | - | - | - | - | - | 19 | NA | NA | NA | - | 3 | 2 | 4, 5 | [44] |
| *COL4A2* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| c.1837G>A, p.Gly613Ser | NA | - | - | - | - | - | 24.7 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4 | [45] |
| c.2105G>A, p.Gly702Asp | NA | - | - | - | - | - | 27.5 | Probably | Tolerated | Deleterious | - | 2, 3 | 1, 2 | 3, 4 | [46] |
| c.2572A>G, p.Ile858Val | NA | - | - | - | - | - | 1.0 | benign | Tolerated | Neutral | - | - | 1, 2 | - | [47] |
| c.2821G>A, p.Gly941Arg | NA | - | - | - | - | - | 26.5 | Probably | Deleterious | Deleterious | - | 2, 3 | 1 | 3, 4 | [48] |
| c.2972G>A, p.Gly991Glu | NA | - | - | - | - | - | 24.8 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4 | [49] |
| c.3110G>A, p.Gly1037Glu | Pathogenic | - | - | - | - | - | 25.7 | Probably | Deleterious | Deleterious | - | 2, 3 | 1, 2 | 3, 4, 5 | [50] |
| c.3206delC | NA | - | - | - | - | - | 33 | NA | NA | NA | 1 |  | 1, 2 | 4 | [51] |
| c.3455G>A, p.Gly1152Asp | Pathogenic | 0.01 | 0 | 0.03 | 0 | 4.8 | 29.4 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [50] |
| c.4165G>A, p.Gly1389Arg | Likely Pathogenic | - | - | - | - | - | 25.5 | Probably | Deleterious | Deleterious | - | 3 | 1, 2 | 3, 4, 5 | [51] |
| p.Ala1534Ser | NA | - | - | - | - | - | 25.7 | Probably | Tolerated | Deleterious | - | - | 2 | 3, 4 | [52] |

CNV, copy number variants; CADD, combined annotation-dependent depletion; probably, probably damaging; possibly damaging; NA, not available.

## Supplementary Table 4. Comparison between CA positive and negative mutations

|  |  |  |  |
| --- | --- | --- | --- |
|  | Positive | Negative | p-value |
| *COL4A1* | n = 18 | n = 22 | - |
| Mutations |  |  |  |
| Missense | 17 (94.4) | 13 (59.1) | 0.0126 |
| G-M-Y | 1 ( 5.6) | 0 (0) | 0.45 |
| G-X-M | 2 (11.1) | 0 (0) | 0.1962 |
| M-X-Y | 13 (72.2) | 12 (54.5) | 0.3319 |
| Charged/Branched-chain AAs | 14 (77.8) | 9 (40.9) | 0.0267 |
| Other than missense mutations | 1 ( 5.6) | 9 (40.9) | 0.0126 |
| 3'UTR | 0 (0) | 4 (18.2) | 0.1135 |
| Frameshift | 0 (0) | 1 (4.5) | 1 |
| Splice Site | 0 (0) | 4 (18.2) | 0.1135 |
| Start Codon | 1 ( 5.6) | 0 (0) | 0.45 |
| Domain |  |  |  |
| 7S | 1 (5.6) | 1 (4.5) | 1 |
| NC1 | 0 (0) | 2 (9.1) | 0.4923 |
| Signal | 1 ( 5.6) | 0 (0) | 0.45 |
| Triple-helical | 16 (88.9) | 15 (68.2) | 0.1489 |
| *COL4A2* | n = 4 | n = 6 | - |
| Mutation type |  |  |  |
| Missense | 4 (100) | 5 (83.3) | 1 |
| G-M-Y | 0 (0) | 1 (16.7) | 1 |
| M-X-Y | 4 (100) | 3 (50.0) | 0.2 |
| Charged/Branched-chain AAs | 4 (100) | 3 (50.0) | 0.2 |
| Frameshift | 0 (0) | 1 (16.7) | 1 |
| Domain |  |  |  |
| NC1 | 0 (0) | 1 (16.7) | 1 |
| Triple-helical | 4 (100) | 5 (83.3) | 1 |

G-M-Y indicates that the mutation is located at the amino acid position after the glycine residue in the glycine triplet sequence. G-X-M indicates that the mutation is located at amino acid position two after the glycine residue in the glycine triplet sequence. M-X-Y indicates that the mutation is located at the glycine position in the glycine triplet sequence. The UTR represents the untranslated region. NC1 represents the noncollagenous domain. AAs are amino acids. CNV is an abbreviation for copy number variant.

## Supplementary Table 5. Comparison of clinical and imaging findings between the CA-positive and CA-negative groups.

|  |  |  |  |
| --- | --- | --- | --- |
|  | CA positive | CA negative | p-value |
|  | n = 25 | n = 51 |  |
| Age at examination, mean ± sd, NA | 37.4 ± 13.9, 7 | 31.2 ± 19.4, 2 | 0.2183 |
| Median [IQR] | 35.5 [24, 50] | 31 [17, 46.5] | - |
| Age at stroke onset, mean ± sd, NA | 32.3 ± 14.0, 13 | 30.2 ± 15.6, 26 | 0.8710 |
|  | 33.5 [21, 42.5] | 34 [17, 43.25] | - |
| Male, n (%), NA | 8 (34.8), 2 | 26 (52.0), 1 | 0.2113 |
| Risk factors |  |  |  |
| HT, n (%), NA | 1 (10),15 | 5 (17.9),23 | 1 |
| Smoking, n (%), NA | 1 (12.5),17 | 6 (50.0),39 | 0.1580 |
| Family history |  |  |  |
| Family history, non-SAH stroke n (%), NA | 13 (61.9), 4 | 17 (40.5), 9 | 0.12 |
| Family history, SAH n (%), NA | 1 (5.0), 5 | 1 (2.6),13 | 1 |
| Family history, CA, n (%), NA | 6 (66.7),16 | 9 (50.0),33 | 0.6828 |
| Region, n (%) |  |  |  |
| Africa | 0 | 1 (2.0) | 0.85586\* |
| Asia | 6 (24.0) | 14 (27.5) |
| Central/South America | 1 (4) | 2 (3.9) |
| Europe | 16 (64.0) | 26 (51.0) |
| Middle East | 0 | 2 (3.9) |
| North America | 2 (8.0) | 5 (9.8) |
| Undetermined | 0 | 1 (2.0) |
| De Novo mutation , n (%) | 4 (16.0) | 9 (17.6) | 1 |
| Stroke | 15 (62.5), 1 | 29 (58.0), 1 | 0.8030 |
| Ischemic stroke n (%), NA | 8 (38.1), 4 | 15 (31.3), 3 | 0.5906 |
| ICH n (%), NA | 5 (22.7), 3 | 14 (29.8), 4 | 0.7731 |
| SAH n (%), NA | 0 (0), 4 | 1 (2.2), 5 | 1 |
| Other stroke n (%), NA | 0 (0), 4 | 0 (0), 5 | 1 |
| Migraine, n (%), NA | 4 (44.4),16 | 1 (6.3), 35 | 0.0403 |
| Cognitive impairments/intellectual abnormality, n (%), NA | 4 (40),15 | 16 (59.3),24 | 0.4597 |
| RAT, n (%), NA | 11 (64.7), 8 | 14 (58.3),27 | 0.7533 |
| Muscle Cramp, n (%), NA | 9 (60.0),10 | 10 (50.0),31 | 0.7338 |
| Nephropathy, n (%), NA | 10 (71.4),11 | 13 (52.0),26 | 0.3172 |
| Seizure, n (%), NA | 2 (28.6),18 | 11 (73.3),36 | 0.0743 |
| Brain imaging findings |  |  |  |
| Structure abnormality of CNS, n (%), NA | 3 (27.3),14 | 15 (46.9),19 | 0.3090 |
| Leukoencephalopathy, n (%), NA | 20 (87.0), 2 | 34 (69.4), 2 | 0.1480 |
| MBs, n (%), NA | 10 (90.9), 14 | 19 (82.6), 28 | 1 |
| Lacunar, n (%), NA | 6 (60.0), 15 | 16 (69.6), 28 | 0.6960 |
| Aneurysm, n (%), NA | 25 (100), 0 | - | - |
| ICA, n (%), NA | 19 (86.4), 3 | - | - |
| MCA, n (%), NA | 1 (4.8), 4 | - | - |
| Acom, n (%), NA | 1 (4.8), 4 | - | - |
| Pcom, n (%), NA | 1 (4.8), 4 | - | - |
| BA, n (%), NA | 2 (9.5), 4 | - | - |
| SCA, n (%), NA | 1 (4.8), 4 | - | - |
| Multiple, n (%), NA | 12 (54.5), 3 | - | - |
| The other large vessel abnormality, n(%), NA | 7 (33.3), 4 | 8 (20.5), 12 | 0.3521 |
| Stenosis/Occlusion, n (%), NA | 3 (15.0), 5 | 3 (7.7), 12 | 0.3976 |
| Dissection, n (%), NA | 1 (4.8), 4 | 0 (0), 12 | 0.3500 |
| Dolichoectasia, n (%), NA | 3 (15.0), 5 | 2 (5.1), 12 | 0.3246 |
| others, n (%), NA | 1 (4.8), 4 | 4 (10.3), 12 | 0.6486 |

CA indicates cerebral aneurysm; HT, hypertension; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; RAT, retinal artery tortuosity; CNS, central nervous system; MBs, microbleeds; MRA, magnetic resonance angiography; CTA, computed tomography angiography; ICA, internal carotid artery; MCA, middle cerebral artery; Acom, anterior communicating artery; Pcom, posterior communicating artery; BA, basilar artery; SCA, superior cerebellar artery; NA, not available. \*Chi-squared tests.

## Supplementary Figure 1. Flow diagram of included publications

ダイアグラム

自動的に生成された説明

## References

1. Magriço, M.; Serôdio, M.; Baptista, M.V. Intracerebral hemorrhage as the sole manifestation of *COL4A1/A2* duplications. *Neurol Sci* **2023**, *44*, 1089-1091, doi:10.1007/s10072-022-06463-4.

2. Renard, D.; Miné, M.; Pipiras, E.; Labauge, P.; Delahaye, A.; Benzacken, B.; Tournier-Lasserve, E. Cerebral small-vessel disease associated with *COL4A1* and *COL4A2* gene duplications. *Neurology* **2014**, *83*, 1029-1031, doi:10.1212/wnl.0000000000000769.

3. Saskin, A.; Sillon, G.; Palfreeman, N.; Buhas, D. *COL4A1/2* CNVs and cerebral small vessel disease Narrowing in on the critical chromosomal region. *Neurology* **2018**, *90*, 1026-1028, doi:10.1212/wnl.0000000000005601.

4. Breedveld, G.; de Coo, I.F.; Lequin, M.H.; Arts, W.F.M.; Heutink, P.; Gould, D.B.; John, S.W.M.; Oostra, B.; Mancini, G.M.S. Novel mutations in three families confirm a major role of *COL4A1* in hereditary porencephaly. *Journal of Medical Genetics* **2006**, *43*, 490-495, doi:10.1136/jmg.2005.035584.

5. Caetano, A.; Barbosa, R.; Costa, J.; Viana-Baptista, M. Incomplete HANAC (Hereditary angiopathy, nephropathy, aneurysms, and muscle cramps) syndrome and the first *COL4A1* gene mutation in Portugal (Portuguese). *Sinapse* **2015**, *15*, 23-26.

6. Traenka, C.; Kloss, M.; Strom, T.; Lyrer, P.; Brandt, T.; Bonati, L.H.; Grond-Ginsbach, C.; Engelter, S. Rare genetic variants in patients with cervical artery dissection. *European Stroke Journal* **2019**, *4*, 355-362, doi:10.1177/2396987319861869.

7. Grond-Ginsbach, C.; Brandt, T.; Kloss, M.; Aksay, S.S.; Lyrer, P.; Traenka, C.; Erhart, P.; Martin, J.J.; Altintas, A.; Siva, A.; et al. Next generation sequencing analysis of patients with familial cervical artery dissection. *Eur Stroke J* **2017**, *2*, 137-143, doi:10.1177/2396987317693402.

8. Kellett, S.; Lemaire, M.; Miller, S.P.; Licht, C.; Yoon, G.; Dlamini, N.; Noone, D. Neonatal stroke and haematuria: Questions and Answers. *Pediatric Nephrology* **2018**, *33*, 805-811, doi:10.1007/s00467-017-3745-x.

9. Faure, C.; Castrale, C.; Benabed, A.; Cognard, P.; Lezé, R.; Castro-Farias, D.; Gérard, M.; Louapre, C.; Paques, M. Structural and functional analysis of retinal vasculature in HANAC syndrome with a novel intronic COL4A1 mutation. *Microvasc Res* **2023**, *145*, 104450, doi:10.1016/j.mvr.2022.104450.

10. Giorgio, E.; Vaula, G.; Bosco, G.; Giacone, S.; Mancini, C.; Calcia, A.; Cavalieri, S.; Di Gregorio, E.; De Longrais, R.R.; Leombruni, S.; et al. Two families with novel missense mutations in *COL4A1*: When diagnosis can be missed. *Journal of the Neurological Sciences* **2015**, *352*, 99-104, doi:10.1016/j.jns.2015.03.042.

11. Alamowitch, S.; Plaisier, E.; Favrole, P.; Prost, C.; Chen, Z.; Van Agtmael, T.; Marro, B.; Ronco, P. Cerebrovascular disease related to *COL4A1* mutations in HANAC syndrome. *Neurology* **2009**, *73*, 1873-1882, doi:10.1212/WNL.0b013e3181c3fd12.

12. Plaisier, E.; Gribouval, O.; Alamowitch, S.; Mougenot, B.; Prost, C.; Verpont, M.C.; Marro, B.; Desmettre, T.; Cohen, S.Y.; Roullet, E.; et al. *COL4A1* mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. *New England Journal of Medicine* **2007**, *357*, 2687-2695, doi:10.1056/NEJMoa071906.

13. Jordan, M.A.; Pierpont, M.E.; Johnston, R.H.; Lee, M.S.; McClelland, C.M. Hereditary Angiopathy With Nephropathy, Aneurysm, and Muscle Cramps (HANAC) Syndrome Presenting to Neuro-Ophthalmology With Metamorphopsia. *J Neuroophthalmol* **2019**, *39*, 506-510, doi:10.1097/wno.0000000000000812.

14. Zenteno, J.C.; Crespi, J.; Buentello-Volante, B.; Buil, J.A.; Bassaganyas, F.; Vela-Segarra, J.I.; Diaz-Cascajosa, J.; Marieges, M.T. Next generation sequencing uncovers a missense mutation in *COL4A1* as the cause of familial retinal arteriolar tortuosity. *Graefes Archive for Clinical and Experimental Ophthalmology* **2014**, *252*, 1789-1794, doi:10.1007/s00417-014-2800-6.

15. Magnin, E.; Ayrignac, X.; Berger, E.; Mine, M.; Tournier-Lasserve, E.; Labauge, P. Late Diagnosis of *COL4A1* Mutation and Problematic Vascular Risk Factor Management. *European Neurology* **2014**, *72*, 150-152, doi:10.1159/000360532.

16. Plaisier, E.; Chen, Z.Y.; Gekeler, F.; Benhassine, S.; Dahan, K.; Marro, B.; Alamowitch, S.; Paques, M.; Ronco, P. Novel *COL4A1* Mutations Associated With HANAC Syndrome: A Role for the Triple Helical CB3 IV Domain. *American Journal of Medical Genetics Part A* **2010**, *152A*, 2550-2555, doi:10.1002/ajmg.a.33659.

17. Coutts, S.B.; Matysiak-Scholze, U.; Kohlhase, J.; Innes, A.M. Intracerebral hemorrhage in a young man. *Canadian Medical Association Journal* **2011**, *183*, E61-E64, doi:10.1503/cmaj.091496.

18. Gulati, A.; Bae, K.T.; Somlo, S.; Watnick, T. Genomic Analysis to Avoid Misdiagnosis of Adults With Bilateral Renal Cysts. *Ann Intern Med* **2018**, *169*, 130-131, doi:10.7326/l17-0644.

19. Wang, Y.; Shi, C.; Li, Y.; Yu, W.; Wei, S.; Fan, Y.; Mao, C.; Yang, Z.; Yu, L.; Zhao, Z.; et al. Genetic Study of Cerebral Small Vessel Disease in Chinese Han Population. *Front Neurol* **2022**, *13*, 829438, doi:10.3389/fneur.2022.829438.

20. Tee, T.Y.; Tan, Y.Y.; Ngu, L.H.; Husin, M.; Nasir, M.N.M.; Ibrahim, K.A.; Aziz, Z.A. Case report of *COL4A1* mutation as monogenic cause of cerebral small vessel disease (Abstract). *International Journal of Stroke* **2022**, *17*, 183-183.

21. Wu, C.; Wang, M.; Wang, X.; Li, W.; Li, S.; Chen, B.; Niu, S.; Tai, H.; Pan, H.; Zhang, Z. The genetic and phenotypic spectra of adult genetic leukoencephalopathies in a cohort of 309 patients. *Brain* **2022**, doi:10.1093/brain/awac426.

22. Corlobe, A.; Tournier-Lasserve, E.; Mine, M.; de Champfleur, N.M.; Dalliere, C.C.; Ayrignac, X.; Labauge, P.; Arquizan, C. *COL4A1* Mutation Revealed by an Isolated Brain Hemorrhage. *Cerebrovascular Diseases* **2013**, *35*, 593-594, doi:10.1159/000351520.

23. Kinoshita, K.; Ishizaki, Y.; Yamamoto, H.; Sonoda, M.; Yonemoto, K.; Kira, R.; Sanefuji, M.; Ueda, A.; Matsui, H.; Ando, Y.; et al. De novo p.G696S mutation in *COL4A1* causes intracranial calcification and late-onset cerebral hemorrhage: A case report and review of the literature. *European Journal of Medical Genetics* **2020**, *63*, doi:10.1016/j.ejmg.2019.103825.

24. Nandeesh, B.N.; Bindu, P.S.; Narayanappa, G.; Yasha, T.C.; Mahadevan, A.; Kulanthaivelu, K.; Santosh, V. Cerebral small vessel disease with hemorrhagic stroke related to *COL4A1* mutation: A case report. *Neuropathology* **2020**, *40*, 93-98, doi:10.1111/neup.12607.

25. Sibon, I.; Coupry, I.; Menegon, P.; Boucher, J.P.; Gorry, P.; Burgelin, I.; Calvas, P.; Orignac, I.; Dousset, V.; Lacombe, D.; et al. *COL4A1* mutation in Axenfeld-Rieger anomaly with leukoencephalopathy and stroke. *Annals of Neurology* **2007**, *62*, 177-184, doi:10.1002/ana.21191.

26. Shah, S.; Kumar, Y.; McLean, B.; Churchill, A.; Stoodley, N.; Rankin, J.; Rizzu, P.; van der Knaap, M.; Jardine, P. A dominantly inherited mutation in *collagen IV A1 (COL4A1)* causing childhood onset stroke without porencephaly. *European Journal of Paediatric Neurology* **2010**, *14*, 182-187, doi:10.1016/j.ejpn.2009.04.010.

27. Rouaud, T.; Labauge, P.; Tournier Lasserve, E.; Mine, M.; Coustans, M.; Deburghgraeve, V.; Edan, G. Acute urinary retention due to a novel collagen *COL4A1* mutation. *Neurology* **2010**, *75*, 747-749, doi:10.1212/WNL.0b013e3181eee440.

28. Deml, B.; Reis, L.M.; Maheshwari, M.; Griffis, C.; Bick, D.; Semina, E.V. Whole exome analysis identifies dominant *COL4A1* mutations in patients with complex ocular phenotypes involving microphthalmia. *Clinical Genetics* **2014**, *86*, 475-481, doi:10.1111/cge.12379.

29. Shah, S.M.; Patel, D.D. *COL4A1* mutation in an Indian child presenting as 'Cerebral Palsy' mimic. *Indian Journal of Radiology and Imaging* **2020**, *30*, 500-503, doi:10.4103/ijri.IJRI\_274\_20.

30. Vahedi, K.; Kubis, N.; Boukobza, M.; Arnoult, M.; Massin, P.; Tournier-Lasserve, E.; Bousser, M.G. *COL4A1* mutation in a patient with sporadic, recurrent intracerebral hemorrhage. *Stroke* **2007**, *38*, 1461-1464, doi:10.1161/STROKEAHA.106.475194.

31. Hatano, T.; Daida, K.; Hoshino, Y.; Li, Y.Z.; Saitsu, H.; Matsumoto, N.; Hattori, N. Dystonia due to bilateral caudate hemorrhage associated with a *COL4A1* mutation. *Parkinsonism & related disorders* **2017**, *40*, 80-82, doi:10.1016/j.parkreldis.2017.04.009.

32. Sasaki, S.; Nozaki, A.; Saitsu, H.; Miyatake, S.; Matsumoto, N.; Kumada, T.; Shibata, M.; Fujii, T. A *COL4A1*-related disorder patient with various findings in the brain imaging (Japanese). *No to Hattatsu* **2017**, *49*, 405-407.

33. Plancher, J.M.; Hufnagel, R.B.; Vagal, A.; Peariso, K.; Saal, H.M.; Broderick, J.P. Case of Small Vessel Disease Associated with *COL4A1* Mutations following Trauma. *Case Rep Neurol* **2015**, *7*, 142-147, doi:10.1159/000431309.

34. Takenouchi, T.; Ohyagi, M.; Torii, C.; Kosaki, R.; Takahashi, T.; Kosaki, K. Porencephaly in a Fetus and HANAC in Her Father: Variable Expression of *COL4A1* Mutation. *American Journal of Medical Genetics Part A* **2015**, *167*, 156-158, doi:10.1002/ajmg.a.36823.

35. Muto, K.; Miyamoto, R.; Terasawa, Y.; Shimatani, Y.; Hara, K.; Kakimoto, T.; Fukumoto, T.; Osaki, Y.; Fujita, K.; Harada, M.; et al. A novel *COL4A1* variant associated with recurrent epistaxis and glioblastoma. *Human Genome Variation* **2021**, *8*, doi:<https://doi.org/10.1038/s41439-021-00150-0>.

36. Niwa, T.; Aida, N.; Osaka, H.; Wada, T.; Saitsu, H.; Imai, Y. Intracranial Hemorrhage and Tortuosity of Veins Detected on Susceptibility-weighted Imaging of a Child with a Type IV Collagen alpha 1 Mutation and Schizencephaly. *Magnetic Resonance in Medical Sciences* **2015**, *14*, 223-226, doi:10.2463/mrms.2014-0060.

37. Leung, M.; Lewis, E.; Humphreys, P.; Miller, E.; Geraghty, M.; Lines, M.; Sell, E. *COL4A1* mutation in a pediatric patient presenting with post-ictal hemiparesis. *Can J Neurol Sci* **2012**, *39*, 654-657, doi:10.1017/s0317167100015420.

38. Shan, L.D.; Peng, J.; Xiao, H.; Wu, L.W.; Duan, H.L.; Pang, N.; Miriam, K.; Yin, F. Clinical features and *COL4A1* genotype of a toddler with hereditary angiopathy with nephropathy, aneurysms and muscle cramps syndrome (Chinese). *Zhongguo Dang Dai Er Ke Za Zhi* **2019**, *21*, 754-760, doi:10.7499/j.issn.1008-8830.2019.08.004.

39. Morsi, A.; Maldonado, A.; Lal, D.; Moosa, A.N.V.; Pestana-Knight, E.; Bingaman, W. Vasospasm Following Hemispherectomy: A Case Report of a Novel Complication. *World neurosurgery* **2020**, *137*, 357-361, doi:10.1016/j.wneu.2020.02.020.

40. Gale, D.P.; Oygar, D.D.; Lin, F.J.; Oygar, P.D.; Khan, N.; Connor, T.M.F.; Lapsley, M.; Maxwell, P.H.; Neild, G.H. A novel *COL4A1* frameshift mutation in familial kidney disease: the importance of the C-terminal NC1 domain of type IV collagen. *Nephrology Dialysis Transplantation* **2016**, *31*, 1908-1914, doi:10.1093/ndt/gfw051.

41. Zhao, Y.Y.; Duan, R.N.; Ji, L.; Liu, Q.J.; Yan, C.Z. Cervical Spinal Involvement in a Chinese Pedigree With Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy Caused by a 3' Untranslated Region Mutation of *COL4A1* Gene. *Stroke* **2019**, *50*, 2307-2313, doi:10.1161/STROKEAHA.119.024875.

42. Grobe-Einsler, M.; Urbach, H.; Paus, S. Recurrent Pontine Strokes in a Young Male. *J Stroke Cerebrovasc Dis* **2020**, *29*, 105386, doi:10.1016/j.jstrokecerebrovasdis.2020.105386.

43. Li, Q.; Wang, C.; Li, W.; Zhang, Z.; Wang, S.; Wupuer, A.; Hu, X.; Wumaier, K.; Zhu, Y.; Li, H.; et al. A Novel Mutation in *COL4A1* Gene in a Chinese Family with Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy. *Transl Stroke Res* **2022**, *13*, 238-244, doi:10.1007/s12975-021-00926-0.

44. Verdura, E.; Herve, D.; Bergametti, F.; Jacquet, C.; Morvan, T.; Prieto-Morin, C.; Mackowiak, A.; Manchon, E.; Hosseini, H.; Cordonnier, C.; et al. Disruption of a miR-29 binding site leading to COL4A1 upregulation causes pontine autosomal dominant microangiopathy with leukoencephalopathy. *Ann Neurol* **2016**, *80*, 741-753, doi:10.1002/ana.24782.

45. Talib, S.; Bhattu, S.; Amjad, S.; Talib, Y.; Sachin, P.; Pranita, B.; Umesh. *COL4A2* brain small vessel disease (A case report of previously unreported mutation) *The Annals of Medical and Health Sciences Research* **2022**.

46. Kollmann, P.; Peeters, A.; Vanakker, O.; Sznajer, Y. 'De novo' *Col4A2* mutation in a patient with migraine, leukoencephalopathy, and small carotid aneurysms. *Journal of Neurology* **2016**, *263*, 2327-2329, doi:10.1007/s00415-016-8280-3.

47. Focke, J.K.; Veltkamp, R.; Bauer, P.; Kraemer, M. Novel heterozygous *COL4A2* variant c.2572A > G, p.(I858V) mimicking Sneddon's and Divry van Bogaert Syndrome. *Journal of Neurology* **2022**, *269*, 5153-5156, doi:10.1007/s00415-022-11111-0.

48. Gunda, B.; Mine, M.; Kovacs, T.; Hornyak, C.; Bereczki, D.; Varallyay, G.; Rudas, G.; Audrezet, M.P.; Tournier-Lasserve, E. *COL4A2* mutation causing adult onset recurrent intracerebral hemorrhage and leukoencephalopathy. *Journal of Neurology* **2014**, *261*, 500-503, doi:10.1007/s00415-013-7224-4.

49. Neri, S.; Ferlazzo, E.; Africa, E.; Versace, P.; Ascoli, M.; Mastroianni, G.; Cianci, V.; Aguglia, U.; Gasparini, S. Novel *COL4A2* mutation causing familial malformations of cortical development. *European Review for Medical and Pharmacological Sciences* **2021**, *25*, 898-905, doi:10.26355/eurrev\_202101\_24658.

50. Yoneda, Y.; Haginoya, K.; Arai, H.; Yamaoka, S.; Tsurusaki, Y.; Doi, H.; Miyake, N.; Yokochi, K.; Osaka, H.; Kato, M.; et al. De novo and inherited mutations in *COL4A2*, encoding the type IV collagen α2 chain cause porencephaly. *Am J Hum Genet* **2012**, *90*, 86-90, doi:10.1016/j.ajhg.2011.11.016.

51. Verbeek, E.; Meuwissen, M.E.C.; Verheijen, F.W.; Govaert, P.P.; Licht, D.J.; Kuo, D.S.; Poulton, C.J.; Schot, R.; Lequin, M.H.; Dudink, J.; et al. *COL4A2* mutation associated with familial porencephaly and small-vessel disease. *European Journal of Human Genetics* **2012**, *20*, 844-851, doi:10.1038/ejhg.2012.20.

52. McHugh, D.C.; Esenwa, C. A Novel *COL4A2* Mutation Associated with Recurrent Strokes. *Journal of Stroke & Cerebrovascular Diseases* **2020**, *29*, doi:10.1016/j.jstrokecerebrovasdis.2020.105156.