Systematic Review of Cerebral Phenotypes Associated with Monogenic Cerebral Small Vessel Disease

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SYSTEMATIC REVIEW AND META-ANALYSIS

Systematic Review of Cerebral Phenotypes Associated With Monogenic Cerebral Small-Vessel Disease

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BACKGROUND: Cerebral small-vessel disease (cSVD) is an important cause of stroke and vascular dementia. Most cases are multifactorial, but an emerging minority have a monogenic cause. While *NOTCH3* is the best-known gene, several others have been reported. We aimed to summarize the cerebral phenotypes associated with these more recent cSVD genes.

METHODS AND RESULTS: We performed a systematic review (PROSPERO [International Prospective Register of Systematic Reviews]: CRD42020196720), searching Medline/Embase (conception to July 2020) for any language publications describing *COL4A1/2*, *TREX1*, *HTRA1*, *ADA2*, or *CTSA* pathogenic variant carriers. We extracted data about individuals' characteristics and clinical and vascular radiological cerebral phenotypes. We summarized phenotype frequencies per gene, comparing patterns across genes. We screened 6485 publications including 402, and extracted data on 390 individuals with *COL4A1*, 123 with *TREX1*, 44 with *HTRA1* homozygous, 41 with *COL4A2*, 346 with *ADA2*, 82 with *HTRA1* heterozygous, and 14 with *CTSA*. Mean age ranged from 15 (*ADA2*) to 59 years (*HTRA1* heterozygotes). Clinical phenotype frequencies varied widely: stroke, 9% (*TREX1*) to 52% (*HTRA1* heterozygotes); cognitive features, 0% (*ADA2*) to 64% (*HTRA1* homozygotes); and psychiatric features, 0% (*COL4A2*; *ADA2*) to 57% (*CTSA*). Among individuals with neuroimaging, vascular radiological phenotypes appeared common, ranging from 62% (*ADA2*) to 100% (*HTRA1* homozygotes; *CTSA*). White matter lesions were the most common pathology, except in *ADA2* and *COL4A2* cases, where ischemic and hemorrhagic lesions dominated, respectively.

CONCLUSIONS: There appear to be differences in cerebral manifestations across cSVD genes. Vascular radiological changes were more common than clinical neurological phenotypes, and present in the majority of individuals with reported neuroimaging. However, these results may be affected by age and biases inherent to case reports. In the future, better characterization of associated phenotypes, as well as insights from population-based studies, should improve our understanding of monogenic cSVD to inform genetic testing, guide clinical management, and help unravel underlying disease mechanisms.

Key Words: Mendelian ■ radiological features ■ small-vessel disease ■ stroke ■ systematic review

Cerebral small-vessel disease (cSVD) is recognized as an important cause of stroke and vascular cognitive impairment worldwide. The term *cSVD* describes a group of pathological processes that affect the small arteries, arterioles, venules, and capillaries within the brain.[1] Features of cSVD on neuroimaging include subcortical infarcts, white matter lesions (WMLs), deep intracerebral hemorrhage (ICH), enlarged perivascular spaces (PVSs), cerebral microbleeds, and brain atrophy.[2] Despite the increase in

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CLINICAL PERSPECTIVE

What Is New?

- We present a large systematic review allowing comparisons to be made across the cerebral manifestations of several cerebral small-vessel disease genes, following a comprehensive search strategy including abstracts and foreign-language papers.
- Neuroimaging appears particularly important in detecting early or otherwise clinically asymptomatic disease (radiological vascular phenotypes were more common than clinical neurological phenotypes).
- Cognitive involvement appeared even more frequently than clinical stroke for several genes.

What Are the Clinical Implications?

- The findings summarized here have clinical implications for the diagnosis of these rare genetic diseases, especially in conjunction with similar summaries of their extracerebral phenotypes published elsewhere, potentially allowing more informed clinical management of symptoms and disease progression.
- There may be a role for radiological screening for earlier diagnosis in patients and at-risk family members, but more research is needed to explore this further.
- The frequency profile of clinical cerebral phenotypes associated with monogenic cerebral small-vessel diseases suggests that it is important to consider a broad spectrum of manifestations when identifying potential patients for genetic testing.

Nonstandard Abbreviations and Acronyms

cSVD	cerebral small-vessel disease
HetZ	heterozygous
HomZ	homozygous or compound heterozygous
ICH	intracerebral hemorrhage
OMIM	Online Mendelian Inheritance in Man
PROSPERO	International Prospective Register of Systematic Reviews
PVSs	perivascular spaces
VEP	Variant Effect Predictor
WMLs	white matter lesions

cSVD burden among an aging population, the underlying disease mechanisms are incompletely understood, and therapeutic options limited, with vascular risk factor management remaining the mainstay of cSVD prevention and treatment.[3]

While the majority of cSVD cases are thought to result from the interaction of multiple genetic variants and environmental factors, an important minority of cases are monogenic, that is, caused by a pathogenic rare variant in a single gene. *NOTCH3* (Notch Receptor 3) is the best known of these genes and is implicated in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[4] However, since NOTCH3 was first described in 1996, several additional cSVD genes have been identified, including *COL4A1* (Collagen, Type Iv, Alpha-1), *TREX1* (3-Prime Repair Exonuclease 1), *HTRA1* (HTRA Serine Peptidase 1), *COL4A2* (Collagen, Type Iv, Alpha-2), *ADA2* (Adenosine Deaminase 2) and, most recently, *CTSA* (Cathepsin A). Pathogenic rare variants in these genes have been associated with various clinical phenotypes alongside cSVD, including extracerebral manifestations (Table 1), as well as certain radiological features seen on neuroimaging.[5]

Better characterization of these rare disorders, including which radiological and clinical phenotypes are associated with specific genes, can inform genetic testing and counseling, including the appropriate selection of patients and screening of family members. This knowledge can also aid in the management of affected individuals, for example, by guiding appropriate screening for certain associated phenotypes. Furthermore, an improved understanding of monogenic cSVD may offer insights into the disease mechanisms underlying sporadic cSVD, as there is increasing evidence to suggest an overlap of disease pathways involved in both sporadic and monogenic disease.[6-8] Observations from large-scale genetic association studies have also shown common variation in monogenic cSVD genes to be associated with sporadic cSVD. Examples include *COL4A2* single-nucleotide polymorphisms' association with lacunar ischemic stroke and deep ICH, *HTRA1* single-nucleotide polymorphism association with ischemic stroke, and possibly association of *NOTCH3* single-nucleotide polymorphisms with WMLs.[9-12]

We undertook a systematic literature review with the aim of identifying all reported individuals with putative pathogenic rare variants in any of the following monogenic cSVD genes: *COL4A1*, *TREX1*, *HTRA1*, *COL4A2*, *ADA2* and *CTSA*. We aimed to summarize and compare both clinical and vascular radiological cerebral phenotypes associated with each monogenic cSVD gene.

METHODS

As a systematic review based on data from published studies, this work does not require approval from an ethical standards committee.

Table 1. Modes of Inheritance and Extracerebral Features for Each Gene

Gene	Mode of inheritance	Extracerebral features
COL4A1/COL4A2	AD	Retinal artery tortuosity*; cataract; kidney cysts; hematuria; muscle cramps and raised creatinine kinase; anterior segment defects; arrhythmia; Raynaud phenomenon; hemolytic anemia
TREX1	AD	Retinal vasculopathy; nephropathy; liver disease; Raynaud phenomenon; skin lesions
HTRA1	AR/AD	Hair loss; degenerative spine disease; back pain
ADA2	AR	Inflammation; skin involvement; liver disease; nephropathy; splenomegaly; myalgia; hematological features
CTSA	AR	Hypertension; dry mouth/eyes; muscle cramps

AD indicates autosomal dominant; and AR, autosomal recessive.
*The relationship between this phenotype and the gene is classed as provisional in the Online Mendelian Inheritance in Man (OMIM) database. Otherwise, all phenotype-genotype relationships are classed as established in OMIM or were taken from the first reporting where not included in the OMIM database (*CTSA*).

Transparency and Openness Promotion Statement

The authors declare that all supporting data are available within the article (and its supplemental material).

Registration

We have registered a PROSPERO (International Prospective Register of Systematic Reviews) protocol (ID: CRD42020196720) at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020196720.[13] We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[14]

Search Strategy

We searched the MEDLINE and EMBASE databases using OvidSP (from conception to July 2020) for publications about individuals with pathogenic rare variants in any of our genes of interest: *COL4A1*, *TREX1*, *HTRA1*, *COL4A2*, *ADA2*, or *CTSA*. We did not restrict the search by language or publication date; we limited it to human studies; and we included conference abstracts. We used a previously published search strategy (Data S1).[5] In summary, the search included:

1. Text words, phrases, and Medical Subject Headings for relevant monogenic syndromes/diseases associated with our genes of interest, and
2. Text words, phrases, and Medical Subject Headings terms associated with cSVD combined with those for our genes of interest and their proteins.

Screening

We carried out the screening using Covidence (www.covidence.org). At least two reviewers (E. W., S. T., L. Y. W. C., D. E. H., B. W., K. R.) independently screened titles and abstracts of all publications identified in our search, blinded to each other's decisions. Full texts of studies included at this stage were then retrieved and screened by 2 reviewers for eligibility, recording any reasons for exclusion. We resolved disagreements through discussion and mutual consensus with a third reviewer. The included publications were combined with those identified via a previous systematic review.[5]

Inclusion/Exclusion Criteria

We included studies that met the following conditions:

1. A case report, case series, or other study design (except review papers) describing the clinical or cerebral radiological phenotype of ≥1 individual. Such description could be anything between stating that the individual was healthy to an in-depth case report.
2. Genetically confirmed rare variant (in a heterozygous [HetZ] or homozygous or compound heterozygous state [HomZ]) in any of our genes of interest.
3. Study authors considered the rare variant to be probably or definitely pathogenic.

We excluded studies describing individuals with rare variants in *CTSA* and *TREX1* associated with galactosialidosis, Aicardi-Goutieres syndrome, and chilblain or systemic lupus. We excluded individuals with a presumed pathogenic variant in >1 gene.

Data Extraction

From each included publication, we (one of E. W., S. T., L. Y. W. C., V. C., E. L., D. E. H., K. R.) extracted data on the first author, publication year, journal, and number of eligible individuals and pedigrees. For foreign language articles, we sought a full translation where an English language abstract did not provide sufficient information or was not available. For each eligible individual, we extracted data using a standardized form, including:

1. The individual's characteristics (region of origin, sex, age at time of assessment); genetic variant, and resulting protein change;
2. Clinical cerebral phenotype (presence, type and age at diagnosis of clinical stroke[s], cognitive features, psychiatric features, and headache);

3. Vascular radiological cerebral phenotype (presence, location, burden, scan type used, age at diagnosis of ischemia, ICH, WMLs, microbleeds, atrophy, enlarged PVSs, calcification, and cerebral aneuryms); and
4. Vascular risk factors (presence of ≥1 of hypertension, smoking, diabetes, excess alcohol consumption, or hypercholesterolemia).

We selected the list of clinical cerebral phenotypes to extract to represent known manifestations of cSVD, including stroke, and the broad categories of cognitive and psychiatric features. We additionally included headache as phenotype of interest because of its association with several monogenic cSVD genes in the Online Mendelian Inheritance in Man (OMIM) database (*ADA2*, *COL4A1*, *TREX1*, and *HTRA1*). Finally, we also noted any other cerebral clinical phenotypes on our data extraction form.

We selected the list of vascular radiological cerebral phenotypes to extract to represent known manifestations of cSVD and again noted any other features on our data extraction form. Finally, we noted any specific radiological patterns to lesion location or severity that might help identify cases in everyday clinical practice.

To assess agreement in data extraction, at least 2 members of the team extracted data from 10% of publications, working independently and blinded to each other's decisions.

Where radiological imaging findings were described, the terminology used across publications varied widely, as has been noted previously in the literature.[2] We made an effort to sort the imaging descriptions into our prespecified categories to deal with the variable terminology (see Data S1 for a list of decisions and assumptions), discussing uncertainties with an expert neuroradiologist (J.W.).

Data Synthesis

For each gene, we summarized the total number of relevant publications, pedigrees, individuals and rare variants, and the individuals' characteristics. We summarized data on the presence or absence of each cerebral phenotype (clinical and vascular radiological) as well as cumulative evidence of any vascular radiological feature, to assess their apparent frequency. We compared findings between genes, highlighting shared patterns and differences in the frequencies of associated phenotypes.

We stratified the presence of clinical stroke and any vascular feature(s) on neuroimaging by presence of ≥1 vascular risk factors. We used the chi-squared test (significance threshold of 0.05) to assess differences in phenotype frequency in patients with and without vascular risk factors.

Variant Pathogenicity Assessment

We used the Ensembl Variant Effect Predictor (VEP)[15] to assess the consequences of the genetic variants included in our systematic review. We extracted information on the variants on the basis of the following VEP subcomponents: (1) SnpEff variant annotation and effect prediction tool to assess variant impact[16]; (2) ClinVar to assess variant's clinical significance[17]; (3) SIFT to predict whether an amino acid substitution is likely to affect protein function[18]; and (4) Polymorphism Phenotyping v2 to predict the effect of an amino acid substitution on the structure and function of a protein.[19] Where conflicting evidence was provided for the same variant (usually because an allele may have a different effect in different transcripts), we selected the category with a more significant/negative effect. We calculated the results (expressed as percentages) among variants per each individual VEP subcomponent.

RESULTS

We included 402 publications from 6485 identified for screening (Figure 1, Supplemental References). As in our previous systematic review,[5] despite only being first reported in 2013, *ADA2* had the largest number of eligible publications (n=149), while the number of publications for other genes appears to be related to their order of discovery (*COL4A1*, n=137; *TREX1*, n=38; *HTRA1*^{HomZ}, n=32; *COL4A2*, n=20; *HTRA1*^{HetZ}, n=32; *CTSA*, n=5) (Figure 2). A likely explanation is the combination of existing treatment options and the severe early-onset systemic phenotype of *ADA2*, prompting more widespread genetic testing. We extracted data on 1040 individuals, with the number of individuals per gene ranging from 14 (*CTSA*) to 390 (*COL4A1*), and the number of pedigrees ranging from 3 (*CTSA*) to 266 (*ADA2*). The percentage of pedigrees carrying a private variant ranged from 0% (*CTSA*) to 76% (*COL4A2*). As expected, the proportion carrying a private variant has decreased since our previous systematic review,[5] presumablybecause of new reported individuals now becoming increasingly likely to have had their rare variant identified previously (Figure 2).

The subset of included studies with data independently extracted for comparison showed 96.3% agreement.

Summary of Individuals' Characteristics

The most common region of origin was Europe for individuals with *COL4A1*, *TREX1*, *COL4A2*, and *CTSA* (67% [263/390], 57% [70/123], 49% [20/41], and 100% [14/14], respectively); Asia for individuals with *HTRA1*^{HomZ} and *HTRA1*^{HetZ} (75% [33/44] and 56% [46/82]); and Turkey for individuals with *ADA2* (28% [98/346]). The region of origin was unknown in 0% to 16% of individuals per gene.

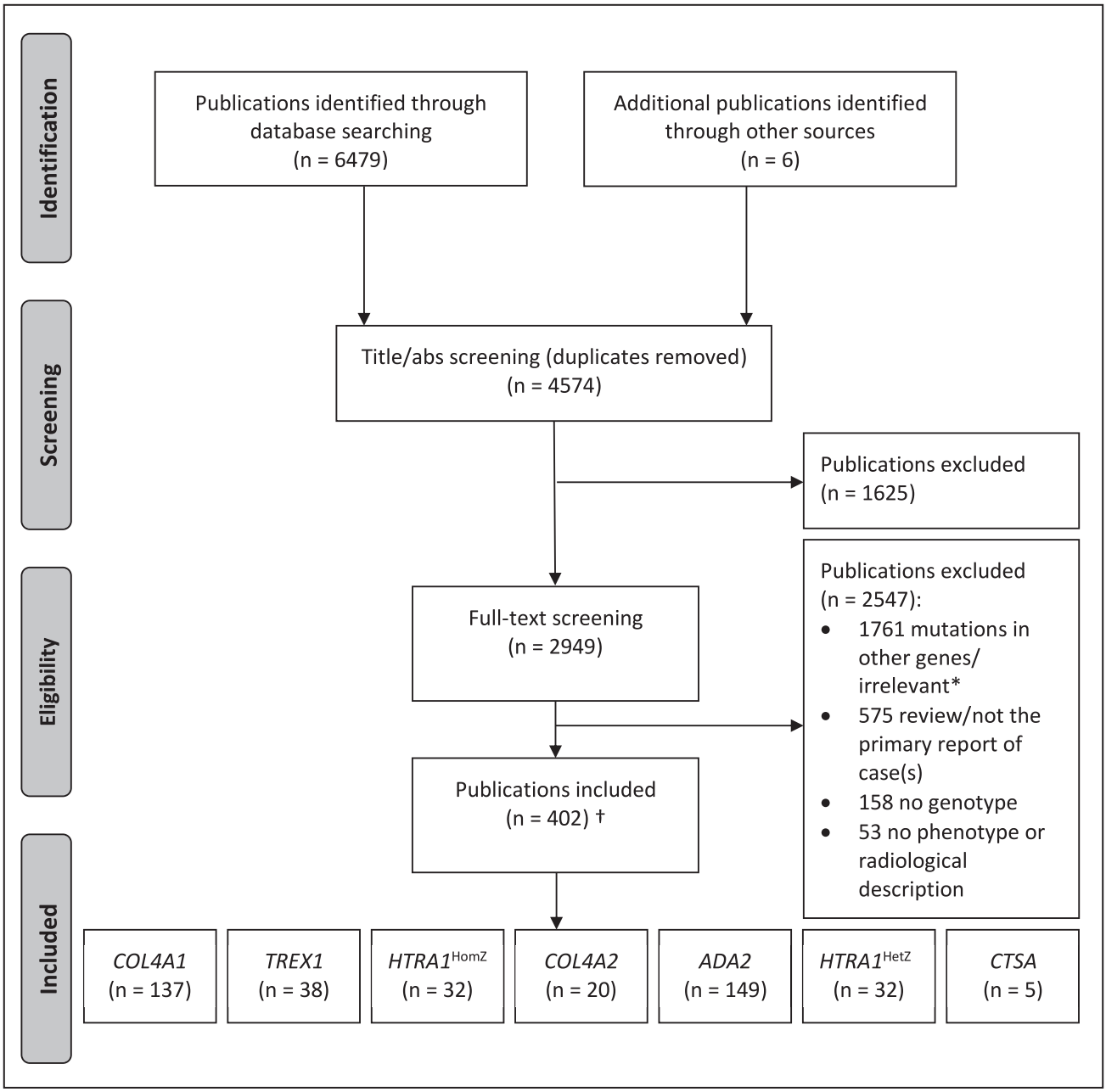

Figure 1. Selection of included publications.
abs indicates abstract; HetZ, heterozygous; and HomZ, homozygous/compound heterozygous. *We identified *NOTCH3*, *FOXC1* and *PITX2* individuals as part of another systematic review. †One publication reported both individuals with *HTRA1*^{HomZ} and individuals with *HTRA1*^{HetZ}, 7 publications reported both individuals with *COL4A1/2*, and 1 publication reported individuals with *HTRA1*^{HetZ}, *COL4A1/2*, and *TREX1*, so the number of unique publications (402) is not the sum of publications per gene (413).

Sex distribution was generally approximated equal (45%–52% female sex) where the number of individuals per gene was considered sufficient to allow meaningful comparison (>100 individuals per gene).

Data about the age of individuals at the time of assessment were not available for >20% of *COL4A1/2* individuals. Mean (median) age ranged from 15 (13) years for individuals with *ADA2* to 59 (60) years for individuals with *HTRA1*^{HetZ}. For *COL4A1/2* and *ADA2*, the median age of individuals was <18 years, while the age ranges were broad (ranging from <1 to 77, 72, and 76, respectively) (Table 2).

Frequency of Clinical Cerebral Phenotypes

Cognitive features were the most common clinical cerebral phenotype for 4 of 7 genes (*HTRA1*^{HomZ},

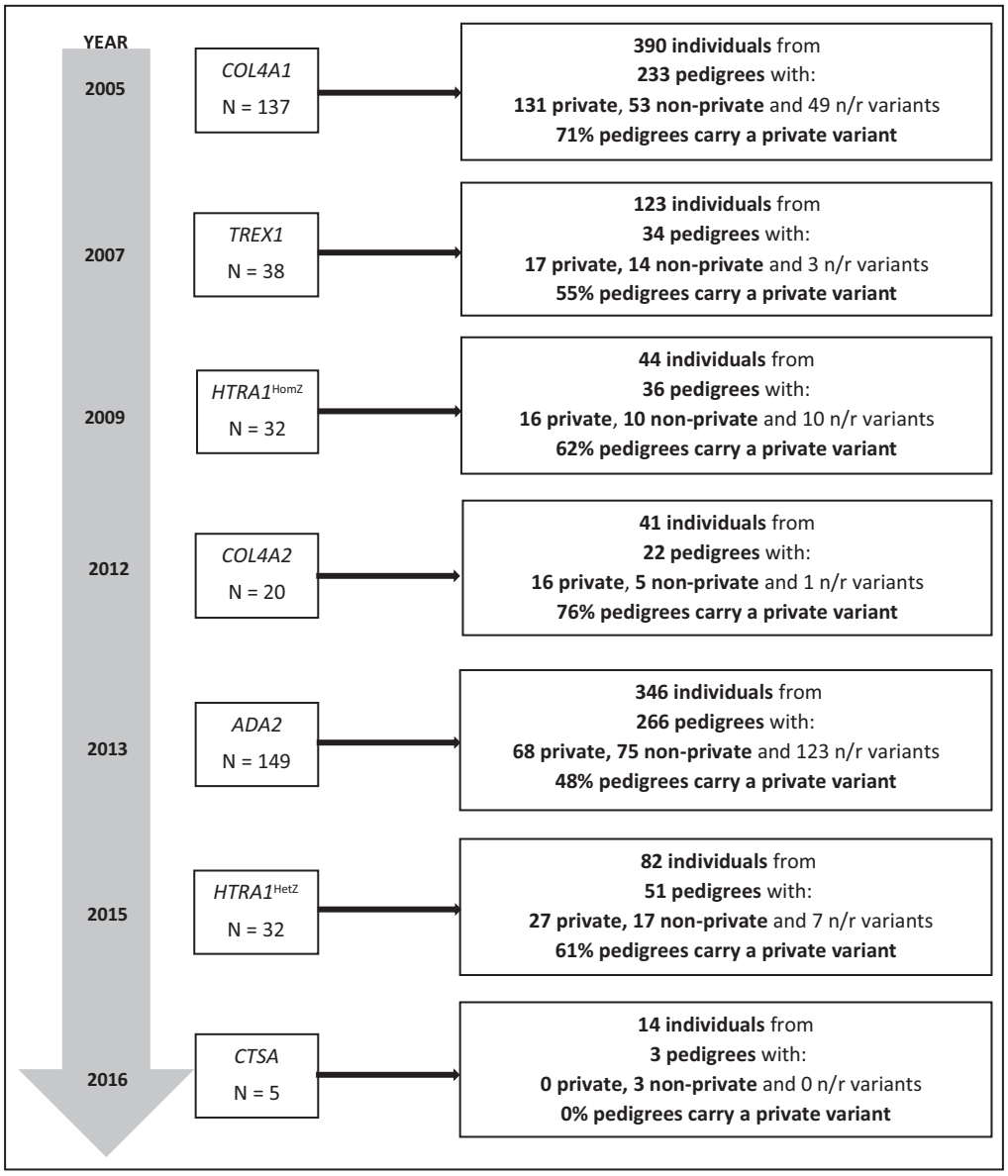

Figure 2. Number of included individuals and pedigrees.
This figure is reporting on DNA change, variant was considered n/r where DNA change was not reported. For compound heterozygotes, if either variant was private, the pedigree was considered to carry a private variant. Where publications had not clearly reported these data (eg, reporting 5 individuals with pathogenic *COL4A1* variants, but not specifying the variants, could refer to 5 individuals all carrying the same variant or each carrying a private variant), we assumed the maximum number of private variants (eg, 5 private variants in this example). HetZ indicates heterozygous; HomZ, homozygous/compound heterozygous; n/r, not reported; and year, year gene first reported to be associated with cSVD.

COL4A2, *HTRA1*^{HetZ}, and *CTSA*); stroke was the most common among individuals with *COL4A1* and *ADA2*, and headache was most common among individuals with *TREX1* (Figure 3, Table S1).

Stroke

The frequency of clinical stroke ranged from 22% to 52% for 6 of 7 genes (*COL4A2*, 22% [9/41]; *HTRA1*^{HomZ}, 30% [13/44]; *ADA2*, 33% [115/346]; *COL4A1*, 41% [161/390]; *CTSA*, 50% [7/14]; *HTRA1*^{HetZ}, 52% [43/82]), while only 9% (11/123) of *TREX1* individuals were reported to have suffered a clinical stroke. Hemorrhagic events (ICH, porencephaly, and intraventricular hemorrhage) were the most commonly reported stroke type among *COL4A1/2* individuals, affecting 73% (118/161) and 100% (9/9) of stroke cases, respectively. Ischemic events (including arterial and venous ischemic stroke, transient ischemic attacks, and ocular

Table 2. Summary of Case Characteristics

	COL4A1 (N=390)	*TREX1* (N=123)	*HTRA1*^{HomZ} (N=44)	*COL4A2* (N=41)	*ADA2* (N=346)	*HTRA1*^{HetZ} (N=82)	*CTSA* (N=14)
Region of origin*							
European	67 (263/390)	57 (70/123)	11 (5/44)	49 (20/41)	27 (95/346)	40 (33/82)	100 (14/14)
Asian	15 (57/390)	14 (17/123)	75 (33/44)	20 (8/41)	18 (62/346)	56 (46/82)	0 (0/14)
Turkish	6 (25/390)	1 (1/123)	7 (3/44)	0 (0/41)	28 (98/346)	2 (2/82)	0 (0/14)
North American	7 (29/390)	24 (30/123)	2 (1/44)	15 (6/41)	6 (21/346)	0 (0/82)	0 (0/14)
South American	0 (0/390)	0 (0/123)	0 (0/44)	0 (0/41)	2 (6/346)	0 (0/82)	0 (0/14)
African	0 (0/390)	0 (0/123)	0 (0/44)	0 (0/41)	2 (8/346)	1 (1/82)	0 (0/14)
Australian	<1 (1/390)	4 (5/123)	5 (2/44)	10 (4/41)	0 (0/346)	0 (0/82)	0 (0/14)
Unknown	4 (15/390)	0 (0/123)	0 (0/44)	7 (3/41)	16 (56/346)	0 (0/82)	0 (0/14)
Sex							
Female/male	52/48 (160/146)	45/55 (54/65)	55/45 (22/18)	38/62 (15/24)	49/51 (132/140)	34/66 (27/52)	86/14 (12/2)
Sex not reported	22 (84/390)	3 (4/123)	9 (4/44)	5 (2/41)	21 (74/346)	4 (3/82)	…
Age at time of assessment†							
Mean, y	22	44	36	23	15	59	57
Median, y	17	…	34	15	13	60	55
Range, y	<1–77	…	24–52	<1–72	<1–76	31–86	39–74
Age *not* reported, %	28	14	11	22	20	10	0

Variables were reported as percentage (proportion). HetZ indicates heterozygous; and HomZ, homozygous/compound heterozygous.

*Region of origin assumed from first author's institution country: 179/390 individuals with *COL4A1*, 19/123 with *TREX1*, 10/44 with *HTRA1*^{HomZ}, 21/41 with *COL4A2*, 152/346 with *ADA2*, and 25/82 with *HTRA1*^{HetZ}. We could not derive this for 15 individuals with *COL4A1*, 3 with *COL4A2*, and 56 with *ADA2*. Individuals reported to have a different region of origin/ancestry from that of the country they lived in were considered to be from their region of origin (eg, Chinese-origin person living in the United States was considered Asian).

†If mean age was available for a group of individuals, the overall summary estimate was weighted by group size. For 78/123 individuals with *TREX1*, only mean age was reported; therefore, they were included in the calculations for mean but not for median age/age range. Turkey was reported on specifically because of high proportion of individuals with *ADA2* from there.

vascular occlusions) were most common for all other genes and were reported in 54% to 100% of stroke cases (*HTRA1*^{HomZ}, 54% [7/13]; *ADA2*, 61% [70/115]; *HTRA1*^{HetZ}, 62% [27/43]; *TREX1*, 82% [9/11]; *CTSA*, 100% [7/7]), although hemorrhagic events also occurred in a substantial minority.

Cognitive Features

The frequency of cognitive features ranged from 27% to 64% for 6 of 7 genes (*COL4A2*, 27% [11/41]; *TREX1*, 29% [36/123]; *COL4A1*, 33% [128/390]; *HTRA1*^{HetZ}, 56% [46/82]; *HTRA1*^{HomZ}, 64% [28/44]; and *CTSA*, 64% [9/14]), while only 2% [7/346] of individuals with *ADA2* were reported to have cognitive features. Developmental delay was present in over 80% of individuals with *COL4A1/2* with cognitive features; however, no cases of developmental delay were reported for other genes. For other genes, publications were generally lacking in detail, so we could not draw conclusions about the nature and severity of cognitive decline (ie, cognitive impairment versus dementia).

Psychiatric Features

The frequency of psychiatric features ranged from 22% to 57% for 4 of 7 genes (*HTRA1*^{HetZ}, 22% [18/82], *TREX1*, 29% [36/124], *HTRA1*^{HomZ}, 32% [14/44], and *CTSA*, 57% [8/14], in ascending order of frequency). The most commonly reported psychiatric features were depression, followed by irritability or agitation. In contrast, only 2% (8/390) of individuals with *COL4A1* reported psychiatric features, and no psychiatric features were reported among individuals with *COL4A2* and *ADA2* (Table S1).

Headache

Headache was reported in 31% (38/123) of *TREX1* individuals and 43% (6/14) of *CTSA* individuals, with >80% of headache cases being specified as migraine. For all other genes, the frequency of headache ranged from 2% to 10%.

Other Clinical Cerebral Phenotypes

Thirty-two percent of individuals with *COL4A1/2* (123/390 and 13/41, respectively) were reported to

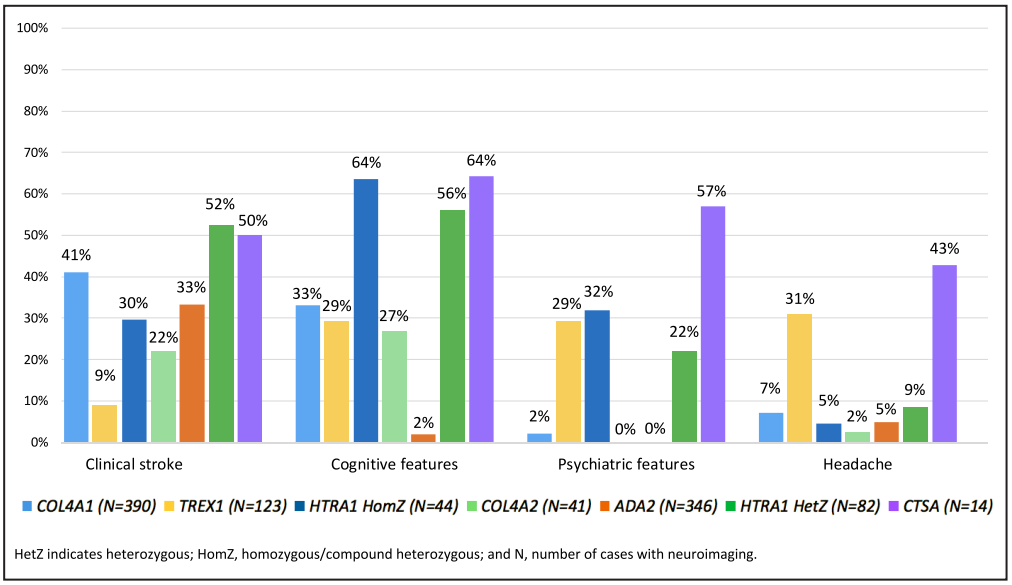

Figure 3. Frequency of clinical cerebral phenotypes by gene.
HetZ indicates heterozygous; and HomZ, homozygous/compound heterozygous.

have suffered a seizure or have epilepsy. Forty-three percent of individuals with (6/14) *CTSA* were reported to suffer from vertigo or balance problems of unclear etiology but suggested to signify brain stem and lower cranial nerve involvement.

Frequency of Radiological Cerebral Phenotypes

The proportion of individuals with neuroimaging (magnetic resonance imaging [MRI], computed tomography, magnetic resonance angiography, or computed tomography angiography) was 74% (290/390) for *COL4A1*, 59% (73/123) for *TREX1*, 100% (44/44) for *HTRA1*^{HomZ}, 76% (31/41) for *COL4A2*, 34% (119/346) for *ADA2*, 85% (70/82) for *HTRA1*^{HetZ}, and 100% (14/14) for *CTSA*. Where neuroimaging was done, it included an MRI scan in 71% to 100% of cases. The rest of this section applies to those with neuroimaging only.

The majority of individuals showed vascular feature(s) on neuroimaging: ≥86% for all genes except *ADA2* (62%). Figure 4 shows the proportion of individuals with specific features suggestive of vascular brain disease, and Table S2 shows the breakdown of these features by location and severity.

Ischemia

Presence ranged from 0% (*COL4A2*) to 66% (*HTRA1*^{HetZ}). Ischemia was the most common radiological manifestation for individuals with *ADA2* (45%). Location was reported for most individuals (80%), and as expected, where reported, was mainly in deep/lacunar areas. Most individuals (70%) had multiple lesions.

Intracerebral Hemorrhage

Presence ranged from 0% (*TREX1*) to 68% (*COL4A2*). It was predominantly present in individuals with *COL4A1/2*. However, ICH was also present in a small minority (7%–10%) of individuals with *HTRA1*, *ADA2*, and *CTSA*. Porencephaly was present in individuals with *COL4A1/2* only (61% and 76%, respectively) and intraventricular hemorrhage was present in individuals with *COL4A1* only (7%). Location, where reported, was mostly deep. The burden is less clear: Single lesions were common, though a minority of individuals did have multiple lesions.

White Matter Lesions

Presence ranged from 3% (*ADA2*) to 100% (*CTSA*). WMLs were the most common radiological manifestation for 5 of 7 genes (not *COL4A2* and *ADA2*). Location was poorly reported, though, where reported, was common in the temporal regions in several genes. Individuals with *CTSA* appear to have lesions mainly in the frontal and parietal regions (though numbers are low). The burden of WMLs, where reported, was mostly severe, though the burden was not reported well (data missing for 51% individuals). The exception to this was individuals with *HTRA1*^{HetZ}, who appear to have less severe WMLs. All individuals with *CTSA* with WMLs with known location had temporal lobe sparing.

Microbleeds

Presence ranged from 1% (*TREX1* and *ADA2*) to 30% (*HTRA1*^{HomZ}). Microbleeds were also common in

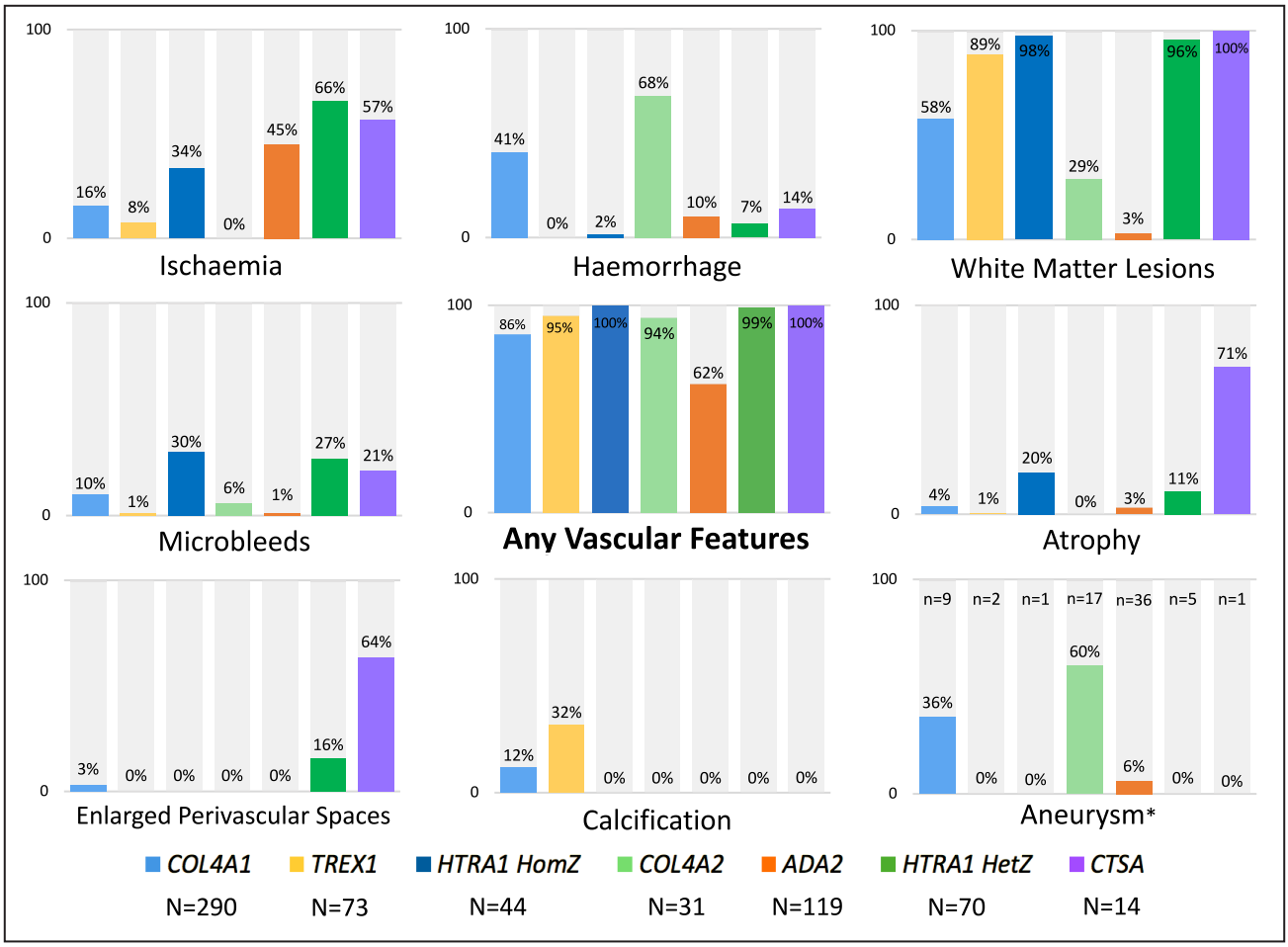

Figure 4. Frequency of radiological cerebral phenotypes by gene.
Hemorrhage: intracerebral hemorrhage, intraventricular hemorrhage or porencephalic cysts. HetZ indicates heterozygous; HomZ, homozygous/compound heterozygous; and N, number of individuals with neuroimaging. Of those with computed tomography angiograms or magnetic resonance angiograms reported are indicated by asterisk (*).

individuals with *HTRA1*^{HetZ} (27%). Location, where reported, was mostly deep. All individuals had multiple lesions where burden was reported.

Atrophy

Presence ranged from 0% (*COL4A2*) to 71% (*CTSA*). Location and burden were poorly described overall, and the low numbers make it difficult to make any conclusions.

Enlarged PVSs

Presence was infrequent: Enlarged PVSs were present in *COL4A1* (3%), *HTRA1*^{HetZ} (16%), and *CTSA* (64%) individuals only.

Calcification

Presence was infrequent: Calcification was present in individuals with *COL4A1/2* only (12% and 32%, respectively).

Cerebral Aneurysm

Present in 36% (13/36) of individuals with *COL4A1*, 60% (3/5) with *COL4A2* and 6% (1/17) with *ADA2* (of those with computed tomography angiograms or magnetic resonance angiograms reported).

Other Radiological Cerebral Phenotypes

Individuals with *COL4A1/2* were also reported to manifest with schizencephaly (8% [24/290] of individuals with *COL4A1* and 13% [4/31] with *COL4A2*) and cerebellar atrophy (5% [14/290] of individuals with *COL4A1* and 3% [1/31] with *COL4A2*). Fifteen percent of individuals with *TREX1* (11/73) had pseudotumoral lesions.

Particular Patterns to Lesion Location or Severity to Help Identify Cases in Practice

A unique feature of individuals with *HTRA1*^{HomZ} was the presence of arc-shaped hyperintense lesions from the

pons to the middle cerebellar peduncles referred to as the "arc sign" (9% [4/44] of individuals) (Figure 5).[20] A unique feature of individuals with *HTRA1*^{HetZ} was the presence of dilated PVSs in the basal ganglia referred to as "status cribrosum" or "état crible" (13% [9/70] individuals) (Figure 6).[2,21] Overall, the descriptions provided were not detailed enough to identify further patterns for other genes.

Vascular Risk Factor Stratification

Fourteen percent (134/928) of individuals across all genes were reported to have ≥1 vascular risk factors. Of these individuals, 62% (88/134) reported clinical stroke, compared with 34% (272/794) of individuals with no reported risk factors (P<0.01), while 78% (104/134) reported vascular features on neuroimaging, compared with 51% (401/794) of individuals with no reported risk factors (P<0.01) (Figure 7). The mean (median) age was 43 (48) years for those with ≥1 risk factor, and 22 (17) years for those with no reported risk factors. This analysis excludes individuals for whom data on risk factors or phenotypes were not available on an individual basis.

Variant Pathogenicity Assessment

VEP produced results from ≥1 of its subcomponents for 15% to 66% of variants overall (SnpEff, 66%; ClinVar, 15%; SIFT, 60%; and Polymorphism Phenotyping v2, 62%), although there was substantial variability for these estimates across different genes. While the percentage of variants with supporting evidence of pathogenicity was high (81%–99%) when studying only the group of variants with data available, this appeared much lower when including all variants regardless of whether VEP was able to process them (12%–65%). Again, there was substantial variability across individual genes (Tables S3 and S4).

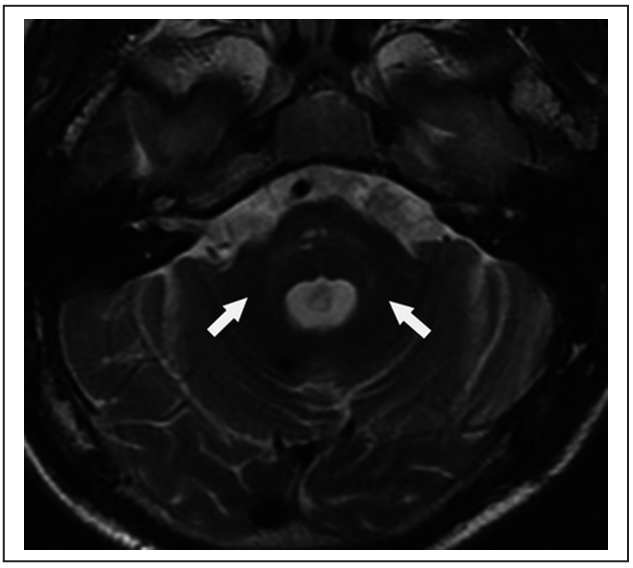

Figure 5. Example of the "arc sign" of the cerebellopontine peduncle on MRI imaging.
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DISCUSSION

Vascular changes are commonly seen on neuroimaging in individuals with rare variant(s) in cSVD genes. Where data are available, the most frequent radiological manifestations are WMLs and ischemic changes and, as expected, most lesions are deep. Common clinical phenotypes include clinical stroke, psychiatric symptoms, and, most frequently reported, cognitive decline. Overall, radiological vascular phenotypes were more common than clinical neurological phenotypes. However, when interpreting these results, it is important to bear in mind that variation in the mean age of affected individuals may explain some of the differences in phenotypes between genes (eg, increased age is a risk factor for both clinical stroke and vascular cerebral phenotypes on neuroimaging).

Both ICH and ischemic stroke were described for all cSVD genes, although the most common stroke subtype was hemorrhagic for *COL4A1/2* and ischemic for the remaining genes. Enlarged perivascular spaces were infrequently reported, which may reflect this feature being less apparent with older imaging modalities, difficult to differentiate from other lesions such as lacunes,[2] or less commonly reported on neuroimaging.

The frequency of both clinical stroke and vascular radiological features on neuroimaging was higher for those with at least 1 vascular risk factor, compared with those with no reported risk factors. However, vascular risk factors were generally poorly reported (therefore, their presence cannot be excluded in most cases), age is highly likely to be a confounding factor, and individuals presenting with stroke/vascular radiological features are more likely to be investigated for vascular risk factors. More research is needed to understand the role for a focused effort on addressing modifiable vascular risk factors in the management of monogenic cSVDs.

We identified only 14 individuals with a putative pathogenic variant in *CTSA*. This is likely (at least partly) explained by the relatively recent description of its association with cSVD, but the small overall number of affected individuals limit the conclusions that can be drawn about its phenotype associations.

The strengths of our study are (1) a comprehensive search strategy, including foreign-language papers and abstracts; (2) systematic data extraction following a preset spreadsheet with a comprehensive list of

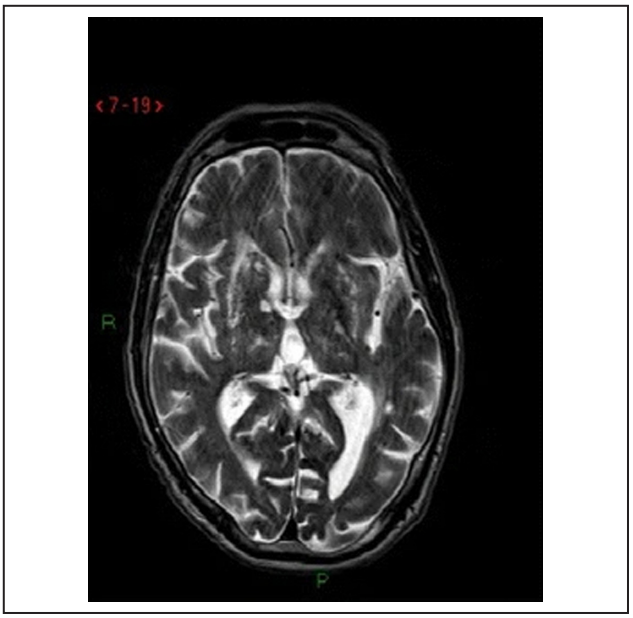

Figure 6. Example of "état crible" on MRI imaging.
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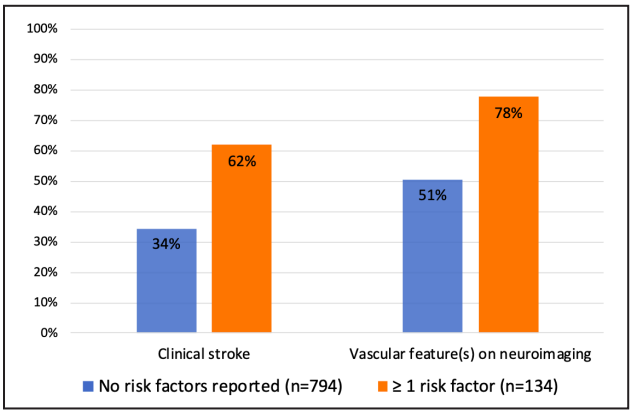

Figure 7. Frequency of cerebral phenotypes, stratified by presence of vascular risk factors.

variables to be collected, while also allowing for novel phenotypes to be recorded; and (3) inclusion of several cSVD genes, allowing comparisons to be made across these.

This research also has some limitations. First, reporting for some variables was poor. For example, region of origin as a marker of ethnicity was frequently poorly reported and therefore often had to be assumed on the basis of information such as the location of the authors' institute. It is possible that some true differences between ethnicities may not have been revealed because of incorrect categorization. Furthermore, individuals from African and South American regions were reported rarely (none reported in 5/7 genes; ≤2% of individuals in 2/7 genes). The understudy of these populations, which comprise over a fifth of the world population, may limit our appreciation of the breadth and frequency of phenotypes that exist. The frequency of neuroimaging reporting was also low for some genes, and it is unknown if neuroimaging was not reported because of lack of positive findings or whether it was not done at all. Second, case reports and case series have many inherent biases that are difficult to control for (eg, testing bias, publication bias, and reporting bias). In addition, the case reports included in this research appeared to lack use of a reporting structure. Current guidelines such as CARE (CAse REports)[24,25] do not work so well in the field of rare genetic diseases, so new, tailored guidelines could help improve the consistency of reporting.

The frequency profile of clinical cerebral phenotypes associated with monogenic cSVDs suggests that it is important to consider a broader spectrum of manifestations when identifying potential patients for genetic testing. Specifically, cognitive involvement appeared even more frequently than clinical stroke for several genes. Our results also show that in monogenic cSVD a radiological vascular phenotype is described more frequently than clinical cerebral phenotypes, suggesting a potential benefit of radiological screening, both for patients and for at-risk family members.

Mancuso et al[26,27] and Guey et al[26,27] provide expert recommendations regarding indications for monogenic cSVD testing in a clinical context. Our work broadly supports these existing recommendations, including "red flag" suggestive clinical and radiological features and age of onset for each gene.

It is also notable that across several monogenic cSVDs, WMLs were commonly identified in the temporal region, a feature that has previously been associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (caused by *NOTCH3* mutations).[28] It is therefore important to also consider other cSVD genes in the presence of this feature.

Finally, according to OMIM (https://www.omim.org), headache is a known phenotype associated with *TREX1* rare variants, thus its high frequency in individuals with *TREX1* was expected. However, other genes associated in OMIM with headache (*COL4A1*, *ADA2*, and *HTRA1*) were not found to have a clear association with this phenotype in our review. Forty-three percent of individuals with *CTSA* (albeit among a total of only 14 individuals) also reported headache, which is more than the expected population prevalence of 15%,[29] suggesting a potentially novel associated phenotype. Epilepsy was another common phenotype in *COL4A1/2*, as suggested by OMIM and previous literature.[30]

VEP predicted 81% to 99% of the processed variants to have a high likelihood of being pathogenic. However, since these percentages are calculated only among variants with data available, this introduces a bias, as some variants without data (eg, synonymous single-nucleotide polymorphisms) have a lower prior likelihood of being pathogenic. Adjusting these calculations to include all variants resulted in only 12% to 65% of variants having supporting evidence of pathogenicity, with substantial variability for results across individual genes. Also, it is possible that some variants have been submitted to ClinVar on the basis of the same case report/case series included in our review. This makes it difficult to draw robust conclusions about included variants' pathogenicity.

The findings summarized here have potential clinical implications for the diagnosis and follow-up of monogenic cSVDs, especially in conjunction with previous data of associated extracerebral phenotypes.[5] Having said this, to get a more comprehensive and less biased overview of the clinical and radiological consequences of monogenic cSVDs, further work should address these same questions using a genotype-first approach (ie, studying this in a population-based setting and among individuals selected on the basis of carrying the variant of interest, regardless of their phenotype). The emergence of prospective population-based studies with biosamples yielding genetic data at scale, such as the UK Biobank (https://www.ukbiobank.ac.uk), will make this possible and complement our study findings.

In summary, we found that individuals with rare variant(s) in our genes of interest appear to develop vascular features on neuroimaging. Clinical stroke and cognitive and psychiatric features are also common. The phenotype profiles appear to differ across monogenic cSVD genes, however, these results may be affected by age and other biases inherent to case reports. In the future, better characterization of associated phenotypes, as well as insights from population-based studies, should improve our understanding of monogenic cSVD to inform genetic testing, guide clinical management, and help unravel underlying disease mechanisms.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S4

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods: Decisions and Assumptions made when extracting data

Demographic data

- Age: sometimes specific ages weren't reported but rather an approximate age or greater/less than a particular age was provided. In these cases we took a best estimation, erring towards overestimating age in some cases so as to minimise overestimation of the burden of the disease in younger brains. For example: <1 = 0, <2 = 1, <27 = 26, ≤26 = 26, early 50s = 52, mid-40s = 45.

Clinical data

- Clinical stroke classification required reporting of symptoms, i.e. not just radiological description
- Intellectual disability was classified under developmental delay

Radiology data

- When scan findings only described 'hemosiderin deposits' we did not take it to mean a confirmed bleed or microbleed
- Cerebral matter loss in <18 year old was recorded as 'other' rather than 'atrophy'
- If a scan was described as showing 'stable findings'/'no changes' or equivalent, we marked the scan as showing the same pathology as the previous scan of the same patient
- In general, author interpretations which used words such as 'probable' or 'suggests' were taken to mean the feature was present, while author interpretations which used words such as 'possible' or 'might be' were not sufficient to consider the feature present
- We took 'periventricular gliosis' to mean white matter lesions
- We classified haemorrhage at the splenium of corpus callosum as 'deep'
- We took 'Hyperintense signal adjacent to the horn of the lateral ventricle' to mean periventricular white matter lesions
- External capsule, internal capsule, centrum semiovale and corona radiata locations qualified as deep
- Punctate hemorrhages were taken to mean brain microbleeds
- Regarding severity of white matter lesions, we assumed the following:
    - 'Severe' when described as: extensive, diffuse, severe, widespread, confluent, Fazekas score 3, disseminated
    - 'Not severe' when described as subtle, early/beginning confluent, limited, moderate, mild, weak, Fazekas score 1 or 2, punctiform
- If a scan was implied but not explicitly stated, we decided whether it was more likely a scan was done than not and assumed based on that – e.g. "haemorrhage in the right frontal area" was taken to mean a scan had been done
- We took a 'petechial spot' to mean a microbleed
- We took porencephalic cysts to be a subcategory of intracerebral haemorrhage

Search Strategy

1. CADASIL/
2. (CADASIL or "Cerebral autosomal dominant arterio$ with subcortical infarct$ and leukoencephalopathy" or (Dementia and hereditary and multi?infarct) or "Familial vascular leukoencephalopathy" or CASIL or "Cerebral arterio$ with subcortical infarct$ and leukoencephalopathy" or "Chronic familial vascular encephalopathy" or "Familial disorder with subcortical ischemic stroke$" or "Agnogenic medial arteriopathy" or "Familial Binswanger$ disease" or (cerebral and autosomal dominant and arterio$ and infarct$ and leukoencephalophy)).af.
3. (CARASIL or "Maeda$ syndrome" or "Cerebral autosomal recessive arterio$ with subcortical infarct$ and leukoencephalopathy" or ("Subcortical Vascular Encephalopathy" and Progressive) or "Cerebrovascular Disease With Thin Skin Alopecia And Disc Disease" or "Nemoto disease" or (cerebral and autosomal recessive and arterio$ and infarct$ and leukoencephalophy) or "Familial young adult onset arterio$ leukoencephalopathy with alopecia and lumbago").af.
4. ((COL4A1$ and (leukoencephalopathy or small vessel disease or autosomal dominant or infantile hemiparesis or retinal arter$ tortuosity or RATOR or PADMAL or "pontine autosomal dominant microangiopathy and leukoencephalopathy" or Walker Warburg or porencephaly 1 or "small vessel disease of the brain with or without ocular abnormalities" or BSVD)) or HANAC or (hereditary angio$ and nephropath$ and aneurysm$ and cramp$) or ((autosomal dominant or familial or hereditary) and (h?ematuria and Retinal Arter$ Tortuosity)) or ("Autosomal dominant familial porencephaly" or "Hereditary multi infarct dementia" or HEMID or hMID) or (multi-infarct dementia and Swedish) or "Nonsyndromic autosomal dominant congenital cataract").af.
5. Muscle Cramp/ and Raynaud Disease/
6. (COL4A2 and (Porencephaly or stroke or Microbleed$ or h?emorrhage or leukoencephalopathy or small vessel disease or autosomal recessive or infantile hemiparesis or retinal arter$ tortuosity)).af.
7. (RVCL or "Retinal vasculopathy with cerebral leukodystrophy" or ($retinal vascul$ and (hereditary or familial)) or ((Cerebroretinal Vasculopathy and Hereditary) or "hereditary vascular retinopathy") or "Grand-Kaine-Fulling syndrome" or HERNS or Hereditary Systemic Angiopathy or (hereditary and endotheliopathy and retin$ and nephro$ and stroke$) or (hereditary and retin$ and (raynaud$ or migraine)) or ADRVCL or (Autosomal Dominant and Retin$ and (leukodystrophy or leukoenchalopathy))).af.
8. ("Early-onset stroke and vasculopathy associated with mutations in ADA2" or (Stroke and vasc$ and ADA2) or ((deficien$ and (ADA 2 or ADA2 or adenosine deaminase-2)) or DADA2 or DADA 2 or (Vasculitis and ADA2 deficien$)) or Sneddon Syndrome or (Polyarteritis nodosa and Childhood onset)).af.

9. (CARASAL or (Cathepsin A related arteriopathy with stroke? and leukoencephalopathy)).af.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (NOTCH?3 or Notch 3 or "Neurogenic locus notch homolog protein 3").af.
12. (TREX?1 or TREX 1 or "Three prime repair exonuclease 1").af.
13. (COL4A1 or COL4A2 or COL4 A1 or COL4 A2 or "COL4 A 1" or "COL4 A 2" or "COL 4 A1" or "COL 4 A2").af.
14. (Collagen and ("type IV" or "type 4") and (alpha?1 or alpha?2 or alpha 1 or alpha 2)).af.
15. Collagen Type IV/
16. (alpha?1 or alpha?2 or alpha 1 or alpha 2).af.
17. 15 and 16
18. (HTRA?1 or HTRA 1 or "HtrA serine peptidase 1" or "HtrA serine protease 1").af.
19. (CECR?1 or CECR 1 or "Cat eye syndrome critical region protein 1" or "adenosine deaminase 2" or ADA2 or ADA 2).af.
20. (FOXC?1 or FOX C1 or FOXC 1 or "FOX C 1" or "forkhead box C?1" or "Forkhead box C 1").af.
21. (PITX?2 or PITX 2 or "paired-like homeodomain 2" or "pituitary homeobox 2" or "Paired-like homeodomain transcription factor 2").af.
22. (Cathepsin?A or Cathepsin A or CathA or Cath A or CTSA).af.
23. 11 or 12 or 13 or 14 or 17 or 18 or 19 or 20 or 21 or 22
24. exp Cerebral Small Vessel Diseases/
25. exp Cerebrovascular Disorders/
26. exp stroke/
27. exp dementia, vascular/
28. Brain Diseases/
29. exp basal ganglia cerebrovascular disease/
30. exp brain ischemia/
31. exp intracranial arterial diseases/
32. exp Cerebral Hemorrhage/
33. exp intracranial hemorrhages/
34. leukomalacia, periventricular/
35. stroke, lacunar/
36. Leukoaraiosis/
37. Leukoencephalopathies/
38. White Matter/
39. Infarction/
40. ("Cerebral Small Vessel Disease?" or cerebrovascular).af.
41. (White matter hyperintensit$ or WMH$ or White matter MR hyperintensit$ or White matter magnetic resonance hyperintensit$ or Subcortical hyperintensit$ or White matter

lesion? or WML$ or Hyper intensit$ or Leukodystroph$ or Leukoaraiosis or Leukomalacia or White Matter Change? or WMC? or White Matter Disease or WMD or White matter damage or Grey matter hyperintensit$ or Brainstem hyperintensit$ or Subcortical hyperintensit$ or White matter hypoattenuation? or White matter hypodensit$ or Leukoencephalopath$).af.
42. (Subcortical infarct? or Cerebral infarct$ or Brain infarct$ or Silent brain infarct$ or Striatocapsular infarct$ or Lacunar infarct$ or Lacune? or Lacunar stroke? or Lacunar syndrome or Stroke? or Vascular lesion?).af.
43. (Microbleed? or Cerebral Microbleed or CMB? or Hypointense lesion? or Subcortical H?emorrhage or Intracerebral h?emorrhage or Cortical siderosis or Superficial siderosis).af.
44. (Perivascular space? or Virchow Robin space? or Type 3 lacune? or Etat crible).af.
45. (Brain atrophy or Cerebral atrophy or Global atrophy or Corpus callosum atrophy or Central atrophy or Mesencephalic atrophy or Hippocampal atrophy or Cortical thinning).af.
46. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 23 and 46
48. 10 or 47
49. limit 48 to humans
50. remove duplicates from 49

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.0
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.6-7; Suppl.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.6-7; Suppl.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.15 para2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p.7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p.7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p.7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p.7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p.15 para2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.8, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1, Suppl.
Study characteristics	17	Cite each included study and present its characteristics.	Suppl.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Suppl.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1, Fig. 2,3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p.15 para 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.14-17
	23b	Discuss any limitations of the evidence included in the review.	p.15
	23c	Discuss any limitations of the review processes used.	p.15-16
	23d	Discuss implications of the results for practice, policy, and future research.	p.16-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.17
Competing interests	26	Declare any competing interests of review authors.	p.17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S1. Frequency and Subtypes of Cerebral Clinical

		COL4A1 (N=390)	*TREX1* (N=123)	*HTRA1*^{HomZ} (N=44)	*COL4A2* (N=41)	*ADA2* (N=346)	*HTRA1*^{HetZ} (N=82)	*CTSA* (N=14)
		% (n/N)						
CLINICAL STROKE	Unknown/ absent	59 (229/390)	91(112/123)	70 (31/44)	78 (32/41)	67(231/346)	48 (39/82)	50 (7/14)
	Present	41 (161/390)	9 (11/123)	30 (13/44)	22 (9/41)	33 (115/346)	52 (43/82)	50 (7/14)
	Ischaemic	15 (24/161)	82 (9/11)	54 (7/13)	0 (0/9)	53 (61/115)	53 (23/43)	71 (5/7)
	Ischaemic	15 (24/161)	73 (8/11)	46 (6/13)	11 (1/9)	55 (63/115)	44 (19/43)	43 (3/7)
	TIA	2 (3/161)	0 (0/11)	8 (1/13)	0 (0/9)	5 (6/115)	14 (6/43)	43 (3/7)
	Eye infarction	0 (0/161)	9 (1/11)	0 (0/13)	0 (0/9)	3 (4/115)	0 (0/43)	14 (1/7)
	Venous thrombosis/infarct	0 (0/161)	0 (0/11)	0 (0/13)	0 (0/9)	0 (0/115)	0 (0/43)	14 (1/7)
	Haemorrhagic	72 (116/161)	0 (0/11)	8 (1/13)	89 (8/9)	12 (14/115)	5 (2/43)	0 (0/7)
	ICH	32 (51/161)	0 (0/11)	8 (1/13)	22 (2/9)	20 (23/115)	14 (6/43)	29 (2/7)
	IVH	4 (7/161)	0 (0/11)	0 (0/13)	0 (0/9)	0 (0/115)	0 (0/43)	0 (0/7)
	Porencephalic cyst	47 (76/161)	0 (0/11)	0 (0/13)	78 (7/9)	0 (0/115)	0 (0/43)	0 (0/7)
	Ischaemic and haemorrhagic	1 (2/161)	0 (0/11)	0 (0/13)	11 (1/9)	8 (9/115)	9 (4/43)	29 (2/7)
	Unspecified/ no detail	12 (19/161)	18 (2/11)	38 (5/13)	0 (0/9)	27 (31 /115)	33 (14/43)	0 (0/7)
COGNITIVE FEATURES	Unknown/ absent	67 (262/390)	71 (87/123)	36 (16/44)	73 (30/41)	100(346/346)	44 (36/82)	36 (5/14)
	Present	33 (128/390)	29 (36/123)	64 (28/44)[#]	27 (11/41)	0 (0/346)	56 (46/82)	64 (9/14)
	Present (≥18 y)	23 (30/131)	34 (36/106)	65 (20/31)	0 (0/13)	0 (0/85)	62 (46/74)	64 (9/14)
	Dementia*	3 (4/128) 17 (5/30)	0 (0/36) 0 (0/36)	32 (9/28) 45 (9/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	13 (6/46) 13 (6/46)	0 (0/9) 0 (0/9)

	Cognitive impairment- no ADL impact*	2 (2/128) 7 (2/30)	0 (0/36) 0 (0/36)	0 (0/28) 0 (0/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	15 (7/46) 15 (7/46)	0 (0/9) 0 (0/9)
	Cognitive impairment- no ADL detail*	12 (15/128) (22/30)	97 (35/36) 100 (35/36)	68 (19/28) 55 (11/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	65 (30/46) 65 (30/46)	100 (9/9) 100 (9/9)
	Subjective cognitive decline*	0 (0/128) 73 (0/30)	0 (0/36) 0 (0/36)	0 (0/28) 0 (0/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	7 (3/46) 7 (3/46)	0 (0/9) 0 (0/9)
	Developmental delay	83 (106/128)	0 (0/36)	0 (0/28)	100 (11/11)	0 (0/0)	0 (0/46)	0 (0/9)
PSYCHIATRIC FEATURES	Unknown/ absent	98 (382/390)	71 (87/123)	68 (30/44)	100 (41/41)	100(346/346)	78 (64/82)	43 (6/14)
	Present	2 (8/390)	29 (36/123)	32 (14/44)	0 (0/41)	0 (0/346)	22 (18/82)	57 (8/14)
	Psychosis	0 (0/8)	6 (2/36)	7 (1/14)	0 (0/0)	0 (0/0)	6 (1/18)	0 (0/8)
	Depression symptoms	25 (2/8)	17 (6/36)	64 (9/14)	0 (0/0)	0 (0/0)	67 (12/18)	88 (7/8)
	Anxiety	0 (0/8)	3 (1/36)	14 (2/14)	0 (0/0)	0 (0/0)	0 (0/18)	0 (0/8)
	Irritability/ agitation	25 (2/8)	8 (3/36)	64 (9/14)	0 (0/0)	0 (0/0)	0 (0/18)	13 (1/8)
	Emotional lability	13 (1/8)	0 (0/36)	21 (3/14)	0 (0/0)	0 (0/0)	28 (5/18)	13 (1/8)
	OCD	0 (0/8)	0 (0/36)	0 (0/14)	0 (0/0)	0 (0/0)	6 (1/18)	0 (0/8)
	Unspecified/ no detail	0 (0/8)	78 (28/36)	0 (0/14)	0 (0/0)	0 (0/0)	0 (0/18)	0 (0/8)
HEADACHE	Unknown/ absent	93 (362/390)	69 (85/123)	95 (42/44)	98 (40/41)	95 (329/346)	91 (75/82)	57 (8/14)
	Present	7 (28/390)	31 (38/123)	5 (2/44)	2 (1/41)	5 (17/346)	9 (7/82)	43 (6/14)
	Migraine	68 (19/28)	84 (32/38)	50 (1/2)	100 (1/1)	24 (4/17)	43 (3/7)	83 (5/6)
	Unspecified	32 (9/28)	16 (6/38)	50 (1/2)	0 (0/1)	76 (13/17)	57 (4/7)	17 (1/6)

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals; n=number of affected individuals; ADL=activities of daily living; #8 cases with unknown age; * second row: only individuals ≥18 years; assumed Stam *et al* cohort were all ≥18 y.

Table S2. Frequency of Vascular Radiological Cerebral Phenotypes by Location and Severity

				COL4A1 (N=290)	*TREX1* (N=73)	*HTRA1*^{HomZ} (N=44)	*COL4A2* (N=31)	*ADA2* (N=119)	*HTRA1*^{HetZ} (N=70)	*CTSA* (N=14)
				% (n/N)						
ISCHAEMIA	Total	Present		16 (47/290)	8 (6/73)	34 (15/44)	0 (0/31)	44 (52/119)	66 (46/70)	57 (8/14)
		Unknown/Absent		84(243/290)	92 (67/73)	66 (29/44)	100(31/31)	56 (67/119)	34 (24/70)	43 (6/14)
	Location	Supratentorial	Deep/ lacunar	43 (20/47)	100 (6/6)	53 (8/15)	0 (0/0)	42 (22/52)	46 (21/46)	75 (6/8)
			Cortical	2 (1/47)	0 (0/6)	0 (0/15)	0 (0/0)	2 (1/52)	2 (1/46)	25 (2/8)
			Unknown	4 (2/47)	0 (0/6)	20 (3/15)	0 (0/0)	10 (5/52)	15 (7/46)	0 (0/8)
		Infratentorial	Brainstem	51 (24/47)	0 (0/6)	53 (8/15)	0 (0/0)	44 (23/52)	26 (12/46)	0 (0/8)
			Cerebellum	2 (1/47)	0 (0/6)	0 (0/15)	0 (0/0)	2 (1/52)	0 (0/46)	25 (2/8)
			Unknown	0 (0/47)	0 (0/6)	0 (0/15)	0 (0/0)	0 (0/52)	0 (0/46)	0 (0/8)
		Overall	Any deep	83 (39/47)	100 (6/6)	67 (10/15)	0 (0/0)	77 (40/52)	78 (36/46)	100 (8/8)
			No deep	2 (1/47)	0 (0/6)	0 (0/15)	0 (0/0)	0 (0/52)	0 (0/46)	0 (0/8)
			Unknown	15 (7/47)	0 (0/6)	33 (5/15)	0 (0/0)	23 (12/52)	22 (10/46)	0 (0/8)
	Burden	Single lesion		2 (1/47)	33 (2/6)	0 (0/15)	0 (0/0)	37 (19/52)	0 (0/46)	50 (4/8)
		Multiple lesions		57 (27/47)	50 (3/6)	87 (13/15)	0 (0/0)	56 (29/52)	100(46/46)	38 (3/8)

		Unknown		40 (19/47)	17 (1/6)	13 (2/15)	0 (0/0)	8 (4/52)	0 (0/46)	13 (1/8)
HAEMORRHAGE	Total	Present		41(118/290)	0 (0/73)	2 (1/44)	68 (21/31)	10 (12/119)	7 (5/70)	7 (1/14)
		Unknown/Absent		59(172/290)	100(73/73)	98 (43/44)	32 (10/31)	90(107/119)	93 (65/70)	93(13/14)
	Porencephaly			61 (72/118)	0 (0/0)	0 (0/1)	76 (16/21)	0 (0/12)	0 (0/5)	0 (0/1)
	IVH			7 (8/118)	0 (0/0)	0 (0/1)	0 (0/21)	0 (0/12)	0 (0/5)	0 (0/1)
	Location	Supratentorial	Deep/ lacunar	25 (29/118)	0 (0/0)	0 (0/1)	14 (3/21)	50 (6/12)	40 (2/5)	100 (1/1)
			Cortical	2 (2/118)	0 (0/0)	0 (0/1)	0 (0/21)	8 (1/12)	0 (0/5)	0 (0/1)
			Unknown	13 (15/118)	0 (0/0)	0 (0/1)	10 (2/21)	42 (5/12)	0 (0/5)	0 (0/1)
		Infratentorial	Brainstem	2 (2/118)	0 (0/0)	0 (0/1)	0 (0/21)	0 (0/12)	20 (1/5)	0 (0/1)
			Cerebellum	6 (7/118)	0 (0/0)	100 (1/1)	0 (0/21)	0 (0/12)	0 (0/5)	0 (0/1)
			Unknown	0 (0/118)	0 (0/0)	0 (0/1)	0 (0/21)	0 (0/12)	0 (0/5)	0 (0/1)
		Overall	Any deep	56 (36/64)	0 (0/0)	100 (1/1)	60 (3/5)	50 (6/12)	60 (3/5)	100 (1/1)
			No deep	3 (2/64)	0 (0/0)	0 (0/1)	0 (0/5)	8 (1/12)	0 (0/5)	0 (0/1)
			Unknown	41 (26/64)	0 (0/0)	0 (0/1)	40 (2/5)	42 (5/12)	40 (2/5)	0 (0/1)

	Burden	Single lesion		45 (53/118)	0 (0/0)	100 (1/1)	76 (16/21)	25 (3/12)	100 (5/5)	100 (1/1)
		Multiple lesions		39 (46/118)	0 (0/0)	0 (0/1)	19 (4/21)	8 (1/12)	0 (0/5)	0 (0/1)
		Unknown		16 (19/118)	0 (0/0)	0 (0/1)	5 (1/21)	67 (8/12)	0 (0/5)	0 (0/1)
WML	Totals	Present		58(167/290)	89 (65/73)	98 (43/44)	29 (9/31)	3 (3/119)	96 (67/70)	100(14/14)
		Unknown/Absent		42(123/290)	11 (8/73)	2 (1/44)	71 (22/31)	97 116/119)	4 (3/70)	0(0/14)
	Location	General	Periventricular only	26 (43/167)	9 (6/65)	0 (0/43)	78 (7/9)	33 (1/3)	7 (5/67)	0 (0/14)
			Deep only	5 (9/167)	2 (1/65)	14 (6/43)	0 (0/9)	33 (1/3)	24 (16/67)	0 (0/14)
			Both	14 (24/167)	2 (1/65)	21 (9/43)	0 (0/9)	0 (0/3)	25 (17/67)	93 (13/14)
			Unknown	54 (91/167)	88 (57/65)	65 (28/43)	22 (2/9)	33 (1/3)	43 (29/67)	7 (1/14)
		Region	Temporal	7 (11/167)	0 (0/65)	30 (13/43)	11 (1/9)	0 (0/3)	7 (5/67)	0 (0/14)
			Frontal	3 (5/167)	0 (0/65)	5 (2/43)	11 (1/9)	0 (0/3)	0 (0/67)	86 (12/14)
			Parietal	2 (3/167)	0 (0/65)	2 (1/43)	0 (0/9)	0 (0/3)	0 (0/67)	86 (12/14)
			Brainstem	2 (3/167)	0 (0/65)	21 (9/43)	0 (0/9)	0 (0/3)	9 (6/67)	7 (1/14)
			Unknown	89(149/167)	100(65/65)	63 (27/43)	89 (8/9)	100 (3/3)	85 (57/67)	7 (1/14)
	Burde	Severe		35 (59/167)	5 (3/65)	95 (41/43)	22 (2/9)	0 (0/3)	12 (8/67)	93 (13/14)
		Not severe		12 (20/167)	3 (2/65)	0 (0/43)	0 (0/9)	0 (0/3)	49 (33/67)	0 (0/14)

		Unknown		53 (88/167)	92 (60/65)	5 (2/43)	78 (7/9)	100 (3/3)	39 (26/67)	7 (1/14)
MICROBLEEDS	Total	Present		10 (29/290)	1 (1/73)	30 (13/44)	6 (2/31)	0 (0/119)	27 (19/70)	21 (3/14)
		Unknown/Absent		90(261/290)	99 (72/73)	70 (31/44)	94 (29/31)	100(119/119)	73 (51/70)	79 (11/14)
	Location	Supratentorial	Deep/ lacunar	52 (15/29)	0 (0/1)	31 (4/13)	50 (1/2)	0 (0/0)	47 (9/19)	100 (3/3)
			Cortical	3 (1/29)	0 (0/1)	8 (1/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)
			Unknown	14 (4/29)	0 (0/1)	46 (6/13)	0 (0/2)	0 (0/0)	26 (5/19)	0 (0/3)
		Infratentorial	Brainstem	21 (6/29)	0 (0/1)	31 (4/13)	0 (0/2)	0 (0/0)	16 (3/19)	33 (1/3)
			Cerebellum	10 (3/29)	0 (0/1)	0 (0/13)	0 (0/2)	0 (0/0)	11 (2/19)	33 (1/3)
			Unknown	3 (1/29)	0 (0/1)	23 (3/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)
		Overall	Any deep	69 (20/29)	0 (0/1)	62 (8/13)	50 (1/2)	0 (0/0)	53 (10/19)	100 (3/3)
			No deep	0 (0/29)	0 (0/1)	0 (0/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)
			Unknown	31 (9/29)	100 (1/1)	38 (5/13)	50 (1/2)	0 (0/0)	47 (9/19)	0 (0/3)
	Burden	Single lesion		14 (4/29)	0 (0/1)	0 (0/13)	0 (0/2)	0 (0/0)	0 (0/19)	33 (1/3)
		Multiple lesions		76 (22/29)	100 (1/1)	85 (11/13)	100 (2/2)	0 (0/0)	100 19/19)	67 (2/3)
		Unknown		10 (3/29)	0 (0/1)	15 (2/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)

CEREBRAL ATROPHY	Total	Present	4 (12/290)	1 (1/73)	20 (9/44)	0 (0/31)	3 (4/119)	11 (8/70)	71 (10/14)
		Unknown/Absent	96(278/290)	99 (72/73)	80 (35/44)	100(31/31)	97 (115/119)	89 (62/70)	29 (4/14)
	Location	Global	25 (3/12)	0 (0/1)	0 (0/9)	0 (0/0)	25 (1/4)	25 (2/8)	0 (0/10)
		Focal	42 (5/12)	0 (0/1)	11 (1/9)	0 (0/0)	25 (1/4)	50(4/8)	10 (1/10)
		Unknown	33 (4/12)	100 (1/1)	89 (8/9)	0 (0/0)	50 (2/4)	25 (2/8)	90 (9/10)
	Burden	Severe	42 (5/12)	0 (0/1)	0 (0/9)	0 (0/0)	0 (0/4)	0 (0/8)	0 (0/10)
		Not severe	0 (0/12)	100 (1/1)	11 (1/9)	0 (0/0)	25 (1/4)	50 (4/8)	90 (9/10)
		Unknown	58 (7/12)	0 (0/1)	89 (8/9)	0 (0/0)	75 (3/4)	50 (4/8)	10 (1/10)
CALCIFICATION	Total	Present	12 (34/290)	32 (23/73)	0 (0/44)	0 (0/31)	0 (0/119)	0 (0/70)	0 (0/14)
		Unknown/Absent	88(256/290)	68 (50/73)	100(44/44)	100(31/31)	100(119/119)	100(70/70)	100(14/14)
ENLARGED PVS	Total	Present	3 (8/290)	0 (0/73)	0 (0/44)	0 (0/31)	0 (0/119)	16 (11/70)	64 (9/14)
		Unknown/Absent	97(282/290)	100(73/73)	100(44/44)	100(31/31)	100(119/119)	84 (59/70)	36 (5/14)
CEREBRAL ANEURYSM	Total	Present	36 (13/36)	0 (0/1)	0 (0/9)	60 (3/5)	6 (1/17)	0 (0/2)	0 (0/1)
		Unknown/Absent	64 (23/36)	100 (1/1)	100 (9/9)	40 (2/5)	94 (16/17)	100 (2/2)	100 (1/1)

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals with neuroimaging; n=number of affected individuals; WML=white matter lesions(s); PVS=perivascular space(s);

Table S3. Variant Effect Predictor Output Summary

Number of variants							% variants with info	% pathogenic* among variants with data	% pathogenic* among all variants
VARIANT IMPACT/CLASSIFICATION OF SEVERITY (SNPEff)									
	no info	low	moderate*	high*					
HTRA1	7	0	35	11			87%	100%	87%
ADA2	43	3	24	18			51%	93%	48%
COL4A1	43	0	88	23			72%	100%	72%
COL4A2	1	0	14	1			94%	100%	94%
TREX1	21	0	2	8			32%	100%	32%
CTSA	1	0	0	0			0%	0%	0%
Total	116	3	163	61			66%	99%	65%
CLINICAL SIGNIFICANCE (ClinVar)									
	no info	uncertain clinical significance	benign	likely benign	likely pathogenic*	pathogenic*			
HTRA1	30	3	0	0	5	15	43%	87%	38%
ADA2	76	2	1	0	6	3	14%	75%	10%
COL4A1	150	1	0	0	0	3	3%	75%	2%
COL4A2	5	0	0	3	3	5	69%	73%	50%
TREX1	29	0	0	0	1	1	6%	100%	6%
CTSA	1	0	0	0	0	0	0%	0%	0%
Total	291	6	1	3	15	27	15%	81%	12%
IMPACT ON PROTEIN FUNCTION (SIFT)									
	no info	tolerated	deleterious*						
HTRA1	18	1	34				66%	97%	64%

ADA2	43	4	41				51%	91%	47%
COL4A1	46	9	99				70%	92%	64%
COL4A2	1	2	13				94%	87%	81%
TREX1	29	1	1				6%	50%	3%
CTSA	1	0	0				0%	0%	0%
Total	138	17	188				60%	92%	55%
IMPACT ON PROTEIN STRUCTURE AND FUNCTION (PolyPhen-2)									
	no info	benign	possibly damaging*	probably damaging*					
HTRA1	18	0	4	31			66%	100%	66%
ADA2	43	5	1	39			51%	89%	45%
COL4A1	40	2	15	97			74%	98%	73%
COL4A2	1	0	4	11			94%	100%	94%
TREX1	29	2	0	0			6%	0%	0%
CTSA	1	0	0	0			0%	0%	0%
Total	132	9	24	178			62%	96%	59%

*category considered to provide supporting evidence for pathogenicity; SnpEff classifies each variant in one of the following output categories: high impact (variant is assumed to have a disruptive impact in the protein, probably causing protein truncation, loss of function or triggering nonsense mediated decay), moderate impact (non-disruptive variant that might change protein effectiveness), and low impact (variant assumed to be mostly harmless or unlikely to change protein behaviour). The 'modifier' category is taken to represent no information about these categories; ClinVar assigns each variant as pathogenic, likely pathogenic, likely benign, benign, or of uncertain clinical significance; SIFT predicts whether an amino acid substitution is likely to affect protein function based on sequence homology and the physico-chemical similarity between the alternate amino acids, concluding with a qualitative prediction if a variant is deleterious or tolerated; PolyPhen-2 predicts the effect of an amino acid substitution on the structure and function of a protein using sequence homology, 3D structures where available, and a number of other databases and tools. It classifies each variant as probably damaging, possibly damaging or benign.

TABLE S4. Variant Effect Predictor outputs per

gene A. *HTRA1*

Genetic mutation	Protein change	Variant information
c.589C>T	p.R197X	Stop gained, likely deleterious, high impact. Pathogenic
c.865C>T	p.Q289X	Stop gained, likely deleterious, high impact. Pathogenic
c.1108C>T	p.R370X	Stop gained, high impact variant. Pathogenic/likely pathogenic
c.904C>T	p.R302X	Stop gained, high impact variant. Likely pathogenic
c.502A.T	p.K168ter	Stop gained, high impact variant
c.847G>T	p.G283Ter	Stop gained, high impact variant
c.983C>A	p.S328*	Stop gained, high impact variant
c.1005+1G>T		Splice donor variant, high impact
c.971A>C	p.N324T	Missense variant, possible splice region variant with moderate impact. Probably damaging to protein structure and conflicting evidence of tolerated/deleterious to protein function. Likely pathogenic
c.754G>A	p.A252T	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Pathogenic
c.956C>T	p.T319I	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.451C>A	p.Q151K	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinial significance
c.359G>A	p.G120D	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic
c.361A>C	p.S121R	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.397C>G	p.R133G	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Possibly damaging to protein structure but tolerated by protein function
c.367G>T	p.A123S	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Only possibly damaging to protein structure and likely to have deleterious effect on protein function
c.821G>A	p.R274Q	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious/some reports of tolerated to protein function. Pathogenic
c.496C>T	p.R166C	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.517G>A	p.A173T	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.517G>C	p.A173P	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.856T>G	p.F286V	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.854C>A	p.P285Q	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic
c.854C>T	p.P285L	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic
c.616G>A	p.G206R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance
c.961G>A	p.A321T	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance
c.1091T>C	p.L364P	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.497G>T	p.R166L	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.614C>G	p.S205C	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic

c.852C>A	p.S284R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.883G>A	p.G295R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.889G>A	p.V297M	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.536T>A	p.I179N	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Likely pathogenic
c.827G>C	p.G276A	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Likely pathogenic
c.1021G>A	p.G341J	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.
c.524T>A	p. V175E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.527T>C	p.V176A	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.646 G>A	p.V216 M	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.847G>A	p.G283R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.848G>A	p.G283E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.850A>G	p.S284G	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.905G>A	p.R302Q	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1348G>C	p.D450H	Missense variant with moderate impact. Only possibly damaging to protein structure and deleterious to protein function.

c.184-185del		Intronic variant, with possible impact on both upstream and downsteam gene regulation, ARMS2. Possible influence on lncRNA.
c.830_831delAG	p.E277Vfs	Intronic variant with possible influence on upstream gene
c.126delG	p.E42fs	Frameshift variant with high impact. Pathogenic
c.543delT	p.A182Pfs*33	Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic
c.739delG	p.E247Rfs	Frameshift mutation with high impact. Potentially leading to premature stop
c.958G>A	p.D320N	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.

B. *ADA2*

Genetic mutation	**Protein change**	**Variant information**
c.982G>A	p.E328K	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene, and CTCF binding site. Probably damaging/benign to protein structure and likely deleterious to protein function/potentially tolerated.
c.138/144delG		5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay
c.37_39del	p.K13del	5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay
c.143_144insG	p.R49Afs*13	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144 dup	p.R49Afs*13	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144_145ins		Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144del	p.R49Gfs*4	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic

c.144delG	p.R49fs	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144dupG	p.R49fs	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.629delT		Frameshift variant, high impact with potential impact on both upstream and downstream genes.
c.427del	p.I143Sfs*41	Frameshift variant, high impact. Impact on nonsense mediated decay transcript processing. Possible impact on downstream genes
c.1447_1451del	p.S483Pfs*5	Intronic variant, possible impact on transcript processing
c.680- 681delAT		Intronic variant, possible impact on transcript processing
c.973-?_1081+?del	p.V325Tfs*7	Intronic variant, possible retained intron. Could have impact on both upstream, downstream genes and nonsense medicated decay transcript processing.
c.972+3A>G		Intronic, splice region variant with low impact. Possible retained intron and impact on nonsense mediated decay transcript processing
c.326C>A	p.A109D	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.336C>A	p.H112Q	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.336C>G	p.H112Q	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.336G>C	p.H112Q	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.962G>A	p.G321E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.133C>T	p.A45T	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.
c.1358A>G	p.Y453C	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.
c.385A>C	p.T129P	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.

c.932T>G	p.L311R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic.
c.1352T>G	p.L451W	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1353G>T	p.L451F	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1360G>C		Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1373T>A	p.V458D	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1223G>A	p.C408Y	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1348G>T	p.G450C	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1367A>G	p.Y456C	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.Pathogenic
c.1065C>A	p.F355L	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Benign protein structure and tolerated by protein function.
c.1052T>A	p.L351Q	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.

c.1057T>C	p.Y353H	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.1069G>A	p.A357T	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.1072G>A	p.G358R	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.1078A>G	p.T360A	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.140G>C	p.G47A	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.278T>C	p.I93T	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.506C>T	p.R169Q	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.506G>A	R169Q	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.533T>C	p.F178S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible retained intron.
c.139G>T	p.G47W	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation, possible impact on processing of pseudogene (FAM32BP). Probably damaging to protein structure and likely to have deleterious effect on protein function.Pathogenic
c.563T>C	p.L188P	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.578C>T	p.P193L	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.139G>A	p.G47R	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting evidence on clinical significance
c.650T>A	p.V217D	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.712G>A	p.D238N	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.872C>T	p.S291L	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.620T>C		Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinical significance
c.791G>C	p.W264S	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging/benign to protein structure and could have deleterious/tolerated impact on protein function. May cause retained intron.
c.1110C>A	p.N370K	Missense variant, moderate impact, possible 3'UTR variant involved in nonsense mediated decay. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.1445A>G		Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1226C>A		Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.752C>T	p.P251L	Missense variant, splice region variant with moderate impact. Possibly damaging to protein structure and tolerated by protein function.
c.424G>A	p.G142S	Missense variant. Change tolerated by protein function, benign impact on protein structure

c.25C>T	p.R9W	Missense variant. Deleterious (but some evidnec of low confidence in finding) to protein function, benign impact on protein structure
c.2T>C	p.M1T	Missense variant. Deleterious (but some evidnec of low confidence in finding) to protein function, benign impact on protein structure
c.73G>T	p.G25C	Missense, splice region variant. Change tolerated by protein function and has benign impact on protein structure
c.882 -2A>G		Splice acceptor variant, high impact . Also potential impact on upstream gene regulation
c.973 -1G>A		Splice acceptor variant, high impact . Also potential regulatory region variant altering TF binding site. Could impact upstream gene regulation (RPL32P5)
c.973 -2A>G		Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay . Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5)
c.973-2A>G		Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay . Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5).
c.542+1G>A		Splice donor variant with high impact. Possible impact on nonsense mediated decay
c.753+2T>A		Splice donor variant with high impact. Possible retained intron
c.753G>A		Splice region variant with low impact. May influence downstream and upstream gene regulation.
c.781delinsCCATA	p.D261Pfs*2	Stop gained, frameshift variant with high impact
c.1196G>A	p.W399*	Stop gained, high impact
c.794C>G	p.Q265X	Stop gained, high impact variant. Possible impact on upstream gene regulation
c.916C>T	p.R306*	Stop gained, high impact variant. Possible impact on upstream gene regulation.
c.660C>A	p.Y220X	Stop gained, high impact variant. Possible impact on upstream gene regulation. Benign.
c.47+2T>C		Synonymous, intron variant with low impact. Potential retained intron

C. *COL4A1*

Genetic mutation	**Protein change**	**Variant information**
c.*35C>A		3' UTR variant, regulatory region variant
c.*31G>T		3'UTR variant, regulatory region variant

c.*32G>A		3'UTR variant, regulatory region variant
c.*32G>T		3'UTR variant, regulatory region variant
c.*33T>A		3'UTR variant, regulatory region variant
c.-2C>T		5'UTR variant, with possible impact on upstream gene regulation
c.2545G>T	p.G808V	Evidence of stop gained, high impact
c.2424delT	p.P810fs	Frameshift mutation with high impact. Potentially leading to premature stop
c.2931dupT	p.G978WfsX15	Frameshift mutation with high impact. Potentially leading to premature stop
c.3702delC	p. G1236*	Frameshift mutation with high impact. Potentially leading to premature stop
c.2085del	p.G696fs	Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic.
c.1121-18G>A		Intronic variant possibly leading to retained intron
c.2645_2646delinsAA	p.G882E	Intronic variant potentially leading to retained intron
c.3877-30C>A		Intronic variant with possible impact on upstream gene regulation. Intron retained
c.4582 -4586 dupCCCATG ins.		Intronic variant, retained intron. Likely deleterious and probably damaging. Possible impact on upstream gene regulation
c.4642T>G	p.C1548G	Missense & splice region variant with low to moderate effect. Likely to impact protein function and probably damaging
c.2969G>A	p.G990E	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.2969G>T	p.G990V	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.3200G>A	p. G1067E	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.3200G>C	p.G1067A	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.3770G>C	p.G1257E	Missense variant in possible regulatory region. Likely deleterious and probably damaging
c.3796G>C	p.G1266R	Missense variant in possible regulatory region. Likely deleterious and probably damaging
c.3832G>T	p.G1278S	Missense variant in possible regulatory region. Likely deleterious and probably damaging. Uncertain clinical significance

c.3245G>A	p.G1082E	Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging
c.3280G>C	p.G1094R	Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging
c.1249G>C	p.G417R	Missense variant with moderate impact. Benign impact on protein structure and deleterious to protein function
c.3997G>A	p.D1333N	Missense variant with moderate impact. Conflicting evidence of effect on protein function, potentially tolerated/potentially deleterious
c.3592G>A	p.G1198R	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3620G>T	p.G1207V	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3656G>A	p. G1219E	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3671C>T	p.P1224L	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3704A>G	p.K1235R	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3706G>A	p.G1236R	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3707G>A	p. G1237E	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3712C>T	p.R1238C	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3505G>A	p. G1169S	Missense variant with moderate impact. Possible splice region variant, with potential impact on downstream gene regulation. Likely deleterious and probably damaging
c.2512A>G	p.M838V	Missense variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.3389G>A	p.G1130D	Missense variant with moderate impact. Potentially modifies upstream and downstream gene regulation. Likely deleterious and probably damaging
c.4088 G > A	p.G1363D	Missense variant with moderate impact. Probably damaging and deleterious to protein function
c.1502G>A		Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1528G>A	p.G510R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1583G>A	p.G528E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function

c.1619A>G	p.K540R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2008G>A	p.G670R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2045G>T	p. G682V	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2063G>A	p.G688D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2078G>A	p.G693E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2086G>A	p.G696S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2086G>T	p.G696C	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2132G>A	p.G711E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2159G>A	p.G720D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2168G>A	p. G723E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2504G>A	p.G835E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.625G>A	p. G209S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.634G>A	p.G212S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1493G>A	p.G498D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic.

c.1493G>T	p.G498V	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic.
c.3383T>A	p.I1128N	Missense variant with moderate impact. Substitution seems to be tolerated by protein function but probably damaging to protein structure
c.3715G>A	p.G1239R	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.3941G>T	p.G1314V	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.3976G>A	p.G1326R	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.3995G>A	p.G1332D	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.4031G>C	p.G1344A	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.4105G>C	p.G1369R	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.4213G>A	p.G1405S	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.1801G>A	p. G601S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function
c.1807C>T	p.P603S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function
c.1555G>A	p.G519R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1835G>A	p.G612D	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1853G > A	p.G618E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2494G>A	p.G832R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2563G>C	p.G855R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2581G>A	p.G861S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2599G>A	p.G867R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.2608G>A	p.G870R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2636G>A	p.G879E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2645G>A	p.G882D	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2662G>A	p.G888R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2689G>A	p.G897S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2699G>A	p.G900E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2744G>A	p.G915E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2782G>C	p.D928H	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2842G>A	p.G948S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2987G>A	p.G996D	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3022G>A	p.G1008R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3040G>C	p.G1014R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3104G>T	p.G1035V	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3122G>A	p.G1041E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.3130G>C	p.G1044E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3190G>A	p.G1064S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.191G>T	p.G64V	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible 3'UTR variant.
c.4739G>C	p.G1580A	Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging
c.4881C>G	p.N1627K	Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging
c.4843G>A	p.E1615K	Missense variant, Moderate impact, possibly retained intron, probably damaging
c.4232G>C	p.G1411A	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4380T>G	p.C1460W	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4652G>A	p. C1551Y	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4717G>A	p.G1573R	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4738 G > A	p.G1580S	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4738G>A	p. G1580S	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.1955G>A	p. G652E	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1963G>A	p.G655R	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.1964G>A	p.G655E	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1973C>A	p. G658V	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1973G>A	p.G658D	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2441 G > T	p.G814V	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.2413G>A	p.G805R	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.2413G>C	p. G805R	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.2317G>A	p.G773R	Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2317G>C	p.G773R	Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2228G>T	p.G743V	Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function
c.2245G>A	p.G749S	Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function
c.2263G>A	p.G755R	Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function
c.4267G>C	p.G1423R	Missense variant, possibly resulting in retained intron. Possibly damaging and likely deleterious to protein function
c.4133G>A	p.G1378D	Missense variant, potentially impacting upstream gene regulation. Likely deleterious and probably damaging

c.4150+1(IVS46) G>T		Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious.
c.4150+1G>A		Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious.
c.4150G>A	p.G1384S	Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious.
c.2345G>C	p.G782A	Missense variant, splice region variant with low-moderate impact. Likely deleterious and probably damaging
c.2096G>A	pG699D	Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure
c.236G>T	p.G79V	Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure
c.443G>A	p.G148E	Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure
c.196C>A	p.Q66K	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.2641A>G	p.M881V	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.3046A>G	p.M1016V	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.31C>A	p.L11M	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.1612C>G	p.R538G	Missense variant. Change tolerated by protein function with benign impact on protein structure
c.1769G>A	p.G562E	Missense variant. Change tolerated by protein function with benign impact on protein structure
c.3946C>G	p.Q1316E	Missense variant. Change tolerated by protein function, likely benign some evidence of possibly damaging protein structure
c.1537-2A>G		Potential frameshift variant and splice acceptor variant with high impact
c.1537–2delA		Potential frameshift variant and splice acceptor variant with high impact
c.1121-2dupA	p.G374_N429 delinsD	Splice acceptor variant, intronic variant leading to retained intron. High impact variant.
c.1382-1G>C		Splice acceptor variant, intronic variant leading to retained intron. High impact variant.
c.2194-1G.A		Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure

c.553-2A>G		Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure and altered downstream gene regulation. Potential 3' UTR variant
c.1990+1G>A		Splice donor variant with high impact. Possible retained intron
c.3406 + 1G>T		Splice donor variant with high impact. Potential impact on both upstream and downstream gene regulation
c.2716 + 1G>A		Splice donor variant with high impact. Potential impact on downstream gene regulation
c.2716+ G>T		Splice donor variant with high impact. Potential impact on downstream gene regulation
c.2716+2T>C		Splice donor variant with high impact. Potential impact on downstream gene regulation
c.2458+1G>A		Splice donor variant, high impact. Possibly retained intron and downstream gene regulation modification
c.1A>T		Start lost, but seems to be tolerated by protein function but possibly damaging to protein structure. Possible impact on upstream gene regulation
c.739C>T	p.Q247*	Stop gained, high impact. Possible modifier of downstream gene regulation
c.607G>T	p. G203R	Stop gained, high impact. Potential 3'UTR regulatory variant
c.4875C>A	p.Y1625*	Stop gained, likely deleterious, high impact
c.4887C>A	p.Y1629X	Stop gained, likely deleterious, high impact
c.1870G>T	p.G624*	Stop gained, likely deleterious, high impact. Possible modifier of downstream gene regulation

D. *COL4A2*

Genetic mutation	**Protein change**	**Variant information**
c.1396G>A	p.G466S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Possible intron variant causing alteration to lncRNA influencing gene AS2
c.1776+1G>A		Splice donor variant with high impact. Possible retained intron and impact to lncRNA influencing gene AS2. Pathogenic but also reported to have uncertain clinical significance
c.1810G>C	p.G604R	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potenital influence on promoter refulation and lncRNA influencing AS2

c.1856G>A	p.G619D	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potenital influence on promoter refulation and lncRNA influencing AS2. Likely pathogenic
c.2105G>A	p.G702D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2399G>A	p.G800E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. With possible impact on upstream gene regulation and promoter regions
c.2821G>A	p.G941R	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Possible retained intron.
c.3110G>A	p.G1037E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic
c.3368A>G	p.E1123G	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Likely benign clinical significance but possible risk factor
c.3448C>A	p.Q1150K	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and tolerated to protein function. Likely benign clinical significance but possible risk factor
c.3455G>A	p.G1152D	Missense variant, splice region variant. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.3490G>A	p.R1164G	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.4129G > A	p.G1377R	Missense variant, moderate impact and potential modifier of upstream gene regulation, possible impact on lncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic
c.4147G>A	p.G1383R	Missense variant, moderate impact and potential modifier of upstream gene regulation, possible impact on lncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic
c.4987G>A	p.G1663S	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation, possible impact on lncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting clinical significane, reported both likely benign and likely pathogenic
c.5068G>A	p.A1690T	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and tolerated to protein function. Likely benign clinical significance but possible risk factor

E. *TREX1*

Genetic mutation	Protein change	Variant information
c.703dup	p.V235GfsX6	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.822delT	p.P275Qfsx2	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.830-833dupAGGA	p.D278fs	Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5
c.829A>T	p.K277*	Stop gained, high impact. Possible modifier of downstream gene regulation. Likely pathogenic.
c.828_831dupGAAG	p.D278EfsTer48	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.703dupG	p.V235Gfs	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.685A>G	p.Arg229Gly	Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and tolerated by protein function
c.690G>T	p.Lys230Asn	Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and could have deleterious effect on protein function, but tolerated also reported
c.581delC	p.Ala194fs	Frameshift variant with high impact, possible downstream gene regulation of ATRIP and SHISA5. Pathogenic
c.742_745dupGTCA	p.T249fs	Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5
c.734dupC	?	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.911_912delCA	p.T304Nfs*12	Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5
c.703_704insG	p.V235GfsX6	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods: Decisions and Assumptions made when extracting data

Demographic data

- Age: sometimes specific ages weren't reported but rather an approximate age or greater/less than a particular age was provided. In these cases we took a best estimation, erring towards overestimating age in some cases so as to minimise overestimation of the burden of the disease in younger brains. For example: <1 = 0, <2 = 1, <27 = 26, ≤26 = 26, early 50s = 52, mid-40s = 45.

Clinical data

- Clinical stroke classification required reporting of symptoms, i.e. not just radiological description
- Intellectual disability was classified under developmental delay

Radiology data

- When scan findings only described 'hemosiderin deposits' we did not take it to mean a confirmed bleed or microbleed
- Cerebral matter loss in <18 year old was recorded as 'other' rather than 'atrophy'
- If a scan was described as showing 'stable findings'/'no changes' or equivalent, we marked the scan as showing the same pathology as the previous scan of the same patient
- In general, author interpretations which used words such as 'probable' or 'suggests' were taken to mean the feature was present, while author interpretations which used words such as 'possible' or 'might be' were not sufficient to consider the feature present
- We took 'periventricular gliosis' to mean white matter lesions
- We classified haemorrhage at the splenium of corpus callosum as 'deep'
- We took 'Hyperintense signal adjacent to the horn of the lateral ventricle' to mean periventricular white matter lesions
- External capsule, internal capsule, centrum semiovale and corona radiata locations qualified as deep
- Punctate hemorrhages were taken to mean brain microbleeds
- Regarding severity of white matter lesions, we assumed the following:
    - 'Severe' when described as: extensive, diffuse, severe, widespread, confluent, Fazekas score 3, disseminated
    - 'Not severe' when described as subtle, early/beginning confluent, limited, moderate, mild, weak, Fazekas score 1 or 2, punctiform
- If a scan was implied but not explicitly stated, we decided whether it was more likely a scan was done than not and assumed based on that – e.g. "haemorrhage in the right frontal area" was taken to mean a scan had been done
- We took a 'petechial spot' to mean a microbleed
- We took porencephalic cysts to be a subcategory of intracerebral haemorrhage

Search Strategy

1. CADASIL/
2. (CADASIL or "Cerebral autosomal dominant arterio$ with subcortical infarct$ and leukoencephalopathy" or (Dementia and hereditary and multi?infarct) or "Familial vascular leukoencephalopathy" or CASIL or "Cerebral arterio$ with subcortical infarct$ and leukoencephalopathy" or "Chronic familial vascular encephalopathy" or "Familial disorder with subcortical ischemic stroke$" or "Agnogenic medial arteriopathy" or "Familial Binswanger$ disease" or (cerebral and autosomal dominant and arterio$ and infarct$ and leukoencephalophy)).af.
3. (CARASIL or "Maeda$ syndrome" or "Cerebral autosomal recessive arterio$ with subcortical infarct$ and leukoencephalopathy" or ("Subcortical Vascular Encephalopathy" and Progressive) or "Cerebrovascular Disease With Thin Skin Alopecia And Disc Disease" or "Nemoto disease" or (cerebral and autosomal recessive and arterio$ and infarct$ and leukoencephalophy) or "Familial young adult onset arterio$ leukoencephalopathy with alopecia and lumbago").af.
4. ((COL4A1$ and (leukoencephalopathy or small vessel disease or autosomal dominant or infantile hemiparesis or retinal arter$ tortuosity or RATOR or PADMAL or "pontine autosomal dominant microangiopathy and leukoencephalopathy" or Walker Warburg or porencephaly 1 or "small vessel disease of the brain with or without ocular abnormalities" or BSVD)) or HANAC or (hereditary angio$ and nephropath$ and aneurysm$ and cramp$) or ((autosomal dominant or familial or hereditary) and (h?ematuria and Retinal Arter$ Tortuosity)) or ("Autosomal dominant familial porencephaly" or "Hereditary multi infarct dementia" or HEMID or hMID) or (multi-infarct dementia and Swedish) or "Nonsyndromic autosomal dominant congenital cataract").af.
5. Muscle Cramp/ and Raynaud Disease/
6. (COL4A2 and (Porencephaly or stroke or Microbleed$ or h?emorrhage or leukoencephalopathy or small vessel disease or autosomal recessive or infantile hemiparesis or retinal arter$ tortuosity)).af.
7. (RVCL or "Retinal vasculopathy with cerebral leukodystrophy" or ($retinal vascul$ and (hereditary or familial)) or ((Cerebroretinal Vasculopathy and Hereditary) or "hereditary vascular retinopathy") or "Grand-Kaine-Fulling syndrome" or HERNS or Hereditary Systemic Angiopathy or (hereditary and endotheliopathy and retin$ and nephro$ and stroke$) or (hereditary and retin$ and (raynaud$ or migraine)) or ADRVCL or (Autosomal Dominant and Retin$ and (leukodystrophy or leukoenchalopathy))).af.
8. ("Early-onset stroke and vasculopathy associated with mutations in ADA2" or (Stroke and vasc$ and ADA2) or ((deficien$ and (ADA 2 or ADA2 or adenosine deaminase-2)) or DADA2 or DADA 2 or (Vasculitis and ADA2 deficien$)) or Sneddon Syndrome or (Polyarteritis nodosa and Childhood onset)).af.

9. (CARASAL or (Cathepsin A related arteriopathy with stroke? and leukoencephalopathy)).af.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (NOTCH?3 or Notch 3 or "Neurogenic locus notch homolog protein 3").af.
12. (TREX?1 or TREX 1 or "Three prime repair exonuclease 1").af.
13. (COL4A1 or COL4A2 or COL4 A1 or COL4 A2 or "COL4 A 1" or "COL4 A 2" or "COL 4 A1" or "COL 4 A2").af.
14. (Collagen and ("type IV" or "type 4") and (alpha?1 or alpha?2 or alpha 1 or alpha 2)).af.
15. Collagen Type IV/
16. (alpha?1 or alpha?2 or alpha 1 or alpha 2).af.
17. 15 and 16
18. (HTRA?1 or HTRA 1 or "HtrA serine peptidase 1" or "HtrA serine protease 1").af.
19. (CECR?1 or CECR 1 or "Cat eye syndrome critical region protein 1" or "adenosine deaminase 2" or ADA2 or ADA 2).af.
20. (FOXC?1 or FOX C1 or FOXC 1 or "FOX C 1" or "forkhead box C?1" or "Forkhead box C 1").af.
21. (PITX?2 or PITX 2 or "paired-like homeodomain 2" or "pituitary homeobox 2" or "Paired-like homeodomain transcription factor 2").af.
22. (Cathepsin?A or Cathepsin A or CathA or Cath A or CTSA).af.
23. 11 or 12 or 13 or 14 or 17 or 18 or 19 or 20 or 21 or 22
24. exp Cerebral Small Vessel Diseases/
25. exp Cerebrovascular Disorders/
26. exp stroke/
27. exp dementia, vascular/
28. Brain Diseases/
29. exp basal ganglia cerebrovascular disease/
30. exp brain ischemia/
31. exp intracranial arterial diseases/
32. exp Cerebral Hemorrhage/
33. exp intracranial hemorrhages/
34. leukomalacia, periventricular/
35. stroke, lacunar/
36. Leukoaraiosis/
37. Leukoencephalopathies/
38. White Matter/
39. Infarction/
40. ("Cerebral Small Vessel Disease?" or cerebrovascular).af.
41. (White matter hyperintensit$ or WMH$ or White matter MR hyperintensit$ or White matter magnetic resonance hyperintensit$ or Subcortical hyperintensit$ or White matter

lesion? or WML$ or Hyper intensit$ or Leukodystroph$ or Leukoaraiosis or Leukomalacia or White Matter Change? or WMC? or White Matter Disease or WMD or White matter damage or Grey matter hyperintensit$ or Brainstem hyperintensit$ or Subcortical hyperintensit$ or White matter hypoattenuation? or White matter hypodensit$ or Leukoencephalopath$).af.
42. (Subcortical infarct? or Cerebral infarct$ or Brain infarct$ or Silent brain infarct$ or Striatocapsular infarct$ or Lacunar infarct$ or Lacune? or Lacunar stroke? or Lacunar syndrome or Stroke? or Vascular lesion?).af.
43. (Microbleed? or Cerebral Microbleed or CMB? or Hypointense lesion? or Subcortical H?emorrhage or Intracerebral h?emorrhage or Cortical siderosis or Superficial siderosis).af.
44. (Perivascular space? or Virchow Robin space? or Type 3 lacune? or Etat crible).af.
45. (Brain atrophy or Cerebral atrophy or Global atrophy or Corpus callosum atrophy or Central atrophy or Mesencephalic atrophy or Hippocampal atrophy or Cortical thinning).af.
46. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 23 and 46
48. 10 or 47
49. limit 48 to humans
50. remove duplicates from 49

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.0
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.6-7; Suppl.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.6-7; Suppl.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.15 para2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p.7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p.7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p.7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p.7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p.15 para2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.8, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1, Suppl.
Study characteristics	17	Cite each included study and present its characteristics.	Suppl.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Suppl.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1, Fig. 2,3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p.15 para 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.14-17
	23b	Discuss any limitations of the evidence included in the review.	p.15
	23c	Discuss any limitations of the review processes used.	p.15-16
	23d	Discuss implications of the results for practice, policy, and future research.	p.16-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.17
Competing interests	26	Declare any competing interests of review authors.	p.17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S1. Frequency and Subtypes of Cerebral Clinical

		COL4A1 (N=390)	*TREX1* (N=123)	*HTRA1*^{HomZ} (N=44)	*COL4A2* (N=41)	*ADA2* (N=346)	*HTRA1*^{HetZ} (N=82)	*CTSA* (N=14)
		% (n/N)						
CLINICAL STROKE	Unknown/ absent	59 (229/390)	91(112/123)	70 (31/44)	78 (32/41)	67(231/346)	48 (39/82)	50 (7/14)
	Present	41 (161/390)	9 (11/123)	30 (13/44)	22 (9/41)	33 (115/346)	52 (43/82)	50 (7/14)
	Ischaemic	15 (24/161)	82 (9/11)	54 (7/13)	0 (0/9)	53 (61/115)	53 (23/43)	71 (5/7)
	Ischaemic	15 (24/161)	73 (8/11)	46 (6/13)	11 (1/9)	55 (63/115)	44 (19/43)	43 (3/7)
	TIA	2 (3/161)	0 (0/11)	8 (1/13)	0 (0/9)	5 (6/115)	14 (6/43)	43 (3/7)
	Eye infarction	0 (0/161)	9 (1/11)	0 (0/13)	0 (0/9)	3 (4/115)	0 (0/43)	14 (1/7)
	Venous thrombosis/infarct	0 (0/161)	0 (0/11)	0 (0/13)	0 (0/9)	0 (0/115)	0 (0/43)	14 (1/7)
	Haemorrhagic	72 (116/161)	0 (0/11)	8 (1/13)	89 (8/9)	12 (14/115)	5 (2/43)	0 (0/7)
	ICH	32 (51/161)	0 (0/11)	8 (1/13)	22 (2/9)	20 (23/115)	14 (6/43)	29 (2/7)
	IVH	4 (7/161)	0 (0/11)	0 (0/13)	0 (0/9)	0 (0/115)	0 (0/43)	0 (0/7)
	Porencephalic cyst	47 (76/161)	0 (0/11)	0 (0/13)	78 (7/9)	0 (0/115)	0 (0/43)	0 (0/7)
	Ischaemic and haemorrhagic	1 (2/161)	0 (0/11)	0 (0/13)	11 (1/9)	8 (9/115)	9 (4/43)	29 (2/7)
	Unspecified/ no detail	12 (19/161)	18 (2/11)	38 (5/13)	0 (0/9)	27 (31 /115)	33 (14/43)	0 (0/7)
COGNITIVE FEATURES	Unknown/ absent	67 (262/390)	71 (87/123)	36 (16/44)	73 (30/41)	100(346/346)	44 (36/82)	36 (5/14)
	Present	33 (128/390)	29 (36/123)	64 (28/44)[#]	27 (11/41)	0 (0/346)	56 (46/82)	64 (9/14)
	Present (≥18 y)	23 (30/131)	34 (36/106)	65 (20/31)	0 (0/13)	0 (0/85)	62 (46/74)	64 (9/14)
	Dementia*	3 (4/128) 17 (5/30)	0 (0/36) 0 (0/36)	32 (9/28) 45 (9/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	13 (6/46) 13 (6/46)	0 (0/9) 0 (0/9)

	Cognitive impairment- no ADL impact*	2 (2/128) 7 (2/30)	0 (0/36) 0 (0/36)	0 (0/28) 0 (0/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	15 (7/46) 15 (7/46)	0 (0/9) 0 (0/9)
	Cognitive impairment- no ADL detail*	12 (15/128) (22/30)	97 (35/36) 100 (35/36)	68 (19/28) 55 (11/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	65 (30/46) 65 (30/46)	100 (9/9) 100 (9/9)
	Subjective cognitive decline*	0 (0/128) 73 (0/30)	0 (0/36) 0 (0/36)	0 (0/28) 0 (0/20)	0 (0/11) 0 (0/0)	0 (0/0) 0 (0/0)	7 (3/46) 7 (3/46)	0 (0/9) 0 (0/9)
	Developmental delay	83 (106/128)	0 (0/36)	0 (0/28)	100 (11/11)	0 (0/0)	0 (0/46)	0 (0/9)
PSYCHIATRIC FEATURES	Unknown/ absent	98 (382/390)	71 (87/123)	68 (30/44)	100 (41/41)	100(346/346)	78 (64/82)	43 (6/14)
	Present	2 (8/390)	29 (36/123)	32 (14/44)	0 (0/41)	0 (0/346)	22 (18/82)	57 (8/14)
	Psychosis	0 (0/8)	6 (2/36)	7 (1/14)	0 (0/0)	0 (0/0)	6 (1/18)	0 (0/8)
	Depression symptoms	25 (2/8)	17 (6/36)	64 (9/14)	0 (0/0)	0 (0/0)	67 (12/18)	88 (7/8)
	Anxiety	0 (0/8)	3 (1/36)	14 (2/14)	0 (0/0)	0 (0/0)	0 (0/18)	0 (0/8)
	Irritability/ agitation	25 (2/8)	8 (3/36)	64 (9/14)	0 (0/0)	0 (0/0)	0 (0/18)	13 (1/8)
	Emotional lability	13 (1/8)	0 (0/36)	21 (3/14)	0 (0/0)	0 (0/0)	28 (5/18)	13 (1/8)
	OCD	0 (0/8)	0 (0/36)	0 (0/14)	0 (0/0)	0 (0/0)	6 (1/18)	0 (0/8)
	Unspecified/ no detail	0 (0/8)	78 (28/36)	0 (0/14)	0 (0/0)	0 (0/0)	0 (0/18)	0 (0/8)
HEADACHE	Unknown/ absent	93 (362/390)	69 (85/123)	95 (42/44)	98 (40/41)	95 (329/346)	91 (75/82)	57 (8/14)
	Present	7 (28/390)	31 (38/123)	5 (2/44)	2 (1/41)	5 (17/346)	9 (7/82)	43 (6/14)
	Migraine	68 (19/28)	84 (32/38)	50 (1/2)	100 (1/1)	24 (4/17)	43 (3/7)	83 (5/6)
	Unspecified	32 (9/28)	16 (6/38)	50 (1/2)	0 (0/1)	76 (13/17)	57 (4/7)	17 (1/6)

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals; n=number of affected individuals; ADL=activities of daily living; #8 cases with unknown age; * second row: only individuals ≥18 years; assumed Stam *et al* cohort were all ≥18 y.

Table S2. Frequency of Vascular Radiological Cerebral Phenotypes by Location and Severity

				COL4A1 (N=290)	*TREX1* (N=73)	*HTRA1*^{HomZ} (N=44)	*COL4A2* (N=31)	*ADA2* (N=119)	*HTRA1*^{HetZ} (N=70)	*CTSA* (N=14)
				% (n/N)						
ISCHAEMIA	Total	Present		16 (47/290)	8 (6/73)	34 (15/44)	0 (0/31)	44 (52/119)	66 (46/70)	57 (8/14)
		Unknown/Absent		84(243/290)	92 (67/73)	66 (29/44)	100(31/31)	56 (67/119)	34 (24/70)	43 (6/14)
	Location	Supratentorial	Deep/ lacunar	43 (20/47)	100 (6/6)	53 (8/15)	0 (0/0)	42 (22/52)	46 (21/46)	75 (6/8)
			Cortical	2 (1/47)	0 (0/6)	0 (0/15)	0 (0/0)	2 (1/52)	2 (1/46)	25 (2/8)
			Unknown	4 (2/47)	0 (0/6)	20 (3/15)	0 (0/0)	10 (5/52)	15 (7/46)	0 (0/8)
		Infratentorial	Brainstem	51 (24/47)	0 (0/6)	53 (8/15)	0 (0/0)	44 (23/52)	26 (12/46)	0 (0/8)
			Cerebellum	2 (1/47)	0 (0/6)	0 (0/15)	0 (0/0)	2 (1/52)	0 (0/46)	25 (2/8)
			Unknown	0 (0/47)	0 (0/6)	0 (0/15)	0 (0/0)	0 (0/52)	0 (0/46)	0 (0/8)
		Overall	Any deep	83 (39/47)	100 (6/6)	67 (10/15)	0 (0/0)	77 (40/52)	78 (36/46)	100 (8/8)
			No deep	2 (1/47)	0 (0/6)	0 (0/15)	0 (0/0)	0 (0/52)	0 (0/46)	0 (0/8)
			Unknown	15 (7/47)	0 (0/6)	33 (5/15)	0 (0/0)	23 (12/52)	22 (10/46)	0 (0/8)
	Burden	Single lesion		2 (1/47)	33 (2/6)	0 (0/15)	0 (0/0)	37 (19/52)	0 (0/46)	50 (4/8)
		Multiple lesions		57 (27/47)	50 (3/6)	87 (13/15)	0 (0/0)	56 (29/52)	100(46/46)	38 (3/8)

		Unknown		40 (19/47)	17 (1/6)	13 (2/15)	0 (0/0)	8 (4/52)	0 (0/46)	13 (1/8)
HAEMORRHAGE	Total	Present		41(118/290)	0 (0/73)	2 (1/44)	68 (21/31)	10 (12/119)	7 (5/70)	7 (1/14)
		Unknown/Absent		59(172/290)	100(73/73)	98 (43/44)	32 (10/31)	90(107/119)	93 (65/70)	93(13/14)
	Porencephaly			61 (72/118)	0 (0/0)	0 (0/1)	76 (16/21)	0 (0/12)	0 (0/5)	0 (0/1)
	IVH			7 (8/118)	0 (0/0)	0 (0/1)	0 (0/21)	0 (0/12)	0 (0/5)	0 (0/1)
	Location	Supratentorial	Deep/ lacunar	25 (29/118)	0 (0/0)	0 (0/1)	14 (3/21)	50 (6/12)	40 (2/5)	100 (1/1)
			Cortical	2 (2/118)	0 (0/0)	0 (0/1)	0 (0/21)	8 (1/12)	0 (0/5)	0 (0/1)
			Unknown	13 (15/118)	0 (0/0)	0 (0/1)	10 (2/21)	42 (5/12)	0 (0/5)	0 (0/1)
		Infratentorial	Brainstem	2 (2/118)	0 (0/0)	0 (0/1)	0 (0/21)	0 (0/12)	20 (1/5)	0 (0/1)
			Cerebellum	6 (7/118)	0 (0/0)	100 (1/1)	0 (0/21)	0 (0/12)	0 (0/5)	0 (0/1)
			Unknown	0 (0/118)	0 (0/0)	0 (0/1)	0 (0/21)	0 (0/12)	0 (0/5)	0 (0/1)
		Overall	Any deep	56 (36/64)	0 (0/0)	100 (1/1)	60 (3/5)	50 (6/12)	60 (3/5)	100 (1/1)
			No deep	3 (2/64)	0 (0/0)	0 (0/1)	0 (0/5)	8 (1/12)	0 (0/5)	0 (0/1)
			Unknown	41 (26/64)	0 (0/0)	0 (0/1)	40 (2/5)	42 (5/12)	40 (2/5)	0 (0/1)

	Burden	Single lesion		45 (53/118)	0 (0/0)	100 (1/1)	76 (16/21)	25 (3/12)	100 (5/5)	100 (1/1)
		Multiple lesions		39 (46/118)	0 (0/0)	0 (0/1)	19 (4/21)	8 (1/12)	0 (0/5)	0 (0/1)
		Unknown		16 (19/118)	0 (0/0)	0 (0/1)	5 (1/21)	67 (8/12)	0 (0/5)	0 (0/1)
WML	Totals	Present		58(167/290)	89 (65/73)	98 (43/44)	29 (9/31)	3 (3/119)	96 (67/70)	100(14/14)
		Unknown/Absent		42(123/290)	11 (8/73)	2 (1/44)	71 (22/31)	97 116/119)	4 (3/70)	0(0/14)
	Location	General	Periventricular only	26 (43/167)	9 (6/65)	0 (0/43)	78 (7/9)	33 (1/3)	7 (5/67)	0 (0/14)
			Deep only	5 (9/167)	2 (1/65)	14 (6/43)	0 (0/9)	33 (1/3)	24 (16/67)	0 (0/14)
			Both	14 (24/167)	2 (1/65)	21 (9/43)	0 (0/9)	0 (0/3)	25 (17/67)	93 (13/14)
			Unknown	54 (91/167)	88 (57/65)	65 (28/43)	22 (2/9)	33 (1/3)	43 (29/67)	7 (1/14)
		Region	Temporal	7 (11/167)	0 (0/65)	30 (13/43)	11 (1/9)	0 (0/3)	7 (5/67)	0 (0/14)
			Frontal	3 (5/167)	0 (0/65)	5 (2/43)	11 (1/9)	0 (0/3)	0 (0/67)	86 (12/14)
			Parietal	2 (3/167)	0 (0/65)	2 (1/43)	0 (0/9)	0 (0/3)	0 (0/67)	86 (12/14)
			Brainstem	2 (3/167)	0 (0/65)	21 (9/43)	0 (0/9)	0 (0/3)	9 (6/67)	7 (1/14)
			Unknown	89(149/167)	100(65/65)	63 (27/43)	89 (8/9)	100 (3/3)	85 (57/67)	7 (1/14)
	Burde	Severe		35 (59/167)	5 (3/65)	95 (41/43)	22 (2/9)	0 (0/3)	12 (8/67)	93 (13/14)
		Not severe		12 (20/167)	3 (2/65)	0 (0/43)	0 (0/9)	0 (0/3)	49 (33/67)	0 (0/14)

		Unknown		53 (88/167)	92 (60/65)	5 (2/43)	78 (7/9)	100 (3/3)	39 (26/67)	7 (1/14)
MICROBLEEDS	Total	Present		10 (29/290)	1 (1/73)	30 (13/44)	6 (2/31)	0 (0/119)	27 (19/70)	21 (3/14)
		Unknown/Absent		90(261/290)	99 (72/73)	70 (31/44)	94 (29/31)	100(119/119)	73 (51/70)	79 (11/14)
	Location	Supratentorial	Deep/ lacunar	52 (15/29)	0 (0/1)	31 (4/13)	50 (1/2)	0 (0/0)	47 (9/19)	100 (3/3)
			Cortical	3 (1/29)	0 (0/1)	8 (1/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)
			Unknown	14 (4/29)	0 (0/1)	46 (6/13)	0 (0/2)	0 (0/0)	26 (5/19)	0 (0/3)
		Infratentorial	Brainstem	21 (6/29)	0 (0/1)	31 (4/13)	0 (0/2)	0 (0/0)	16 (3/19)	33 (1/3)
			Cerebellum	10 (3/29)	0 (0/1)	0 (0/13)	0 (0/2)	0 (0/0)	11 (2/19)	33 (1/3)
			Unknown	3 (1/29)	0 (0/1)	23 (3/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)
		Overall	Any deep	69 (20/29)	0 (0/1)	62 (8/13)	50 (1/2)	0 (0/0)	53 (10/19)	100 (3/3)
			No deep	0 (0/29)	0 (0/1)	0 (0/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)
			Unknown	31 (9/29)	100 (1/1)	38 (5/13)	50 (1/2)	0 (0/0)	47 (9/19)	0 (0/3)
	Burden	Single lesion		14 (4/29)	0 (0/1)	0 (0/13)	0 (0/2)	0 (0/0)	0 (0/19)	33 (1/3)
		Multiple lesions		76 (22/29)	100 (1/1)	85 (11/13)	100 (2/2)	0 (0/0)	100 19/19)	67 (2/3)
		Unknown		10 (3/29)	0 (0/1)	15 (2/13)	0 (0/2)	0 (0/0)	0 (0/19)	0 (0/3)

CEREBRAL ATROPHY	Total	Present	4 (12/290)	1 (1/73)	20 (9/44)	0 (0/31)	3 (4/119)	11 (8/70)	71 (10/14)
		Unknown/Absent	96(278/290)	99 (72/73)	80 (35/44)	100(31/31)	97 (115/119)	89 (62/70)	29 (4/14)
	Location	Global	25 (3/12)	0 (0/1)	0 (0/9)	0 (0/0)	25 (1/4)	25 (2/8)	0 (0/10)
		Focal	42 (5/12)	0 (0/1)	11 (1/9)	0 (0/0)	25 (1/4)	50(4/8)	10 (1/10)
		Unknown	33 (4/12)	100 (1/1)	89 (8/9)	0 (0/0)	50 (2/4)	25 (2/8)	90 (9/10)
	Burden	Severe	42 (5/12)	0 (0/1)	0 (0/9)	0 (0/0)	0 (0/4)	0 (0/8)	0 (0/10)
		Not severe	0 (0/12)	100 (1/1)	11 (1/9)	0 (0/0)	25 (1/4)	50 (4/8)	90 (9/10)
		Unknown	58 (7/12)	0 (0/1)	89 (8/9)	0 (0/0)	75 (3/4)	50 (4/8)	10 (1/10)
CALCIFICATION	Total	Present	12 (34/290)	32 (23/73)	0 (0/44)	0 (0/31)	0 (0/119)	0 (0/70)	0 (0/14)
		Unknown/Absent	88(256/290)	68 (50/73)	100(44/44)	100(31/31)	100(119/119)	100(70/70)	100(14/14)
ENLARGED PVS	Total	Present	3 (8/290)	0 (0/73)	0 (0/44)	0 (0/31)	0 (0/119)	16 (11/70)	64 (9/14)
		Unknown/Absent	97(282/290)	100(73/73)	100(44/44)	100(31/31)	100(119/119)	84 (59/70)	36 (5/14)
CEREBRAL ANEURYSM	Total	Present	36 (13/36)	0 (0/1)	0 (0/9)	60 (3/5)	6 (1/17)	0 (0/2)	0 (0/1)
		Unknown/Absent	64 (23/36)	100 (1/1)	100 (9/9)	40 (2/5)	94 (16/17)	100 (2/2)	100 (1/1)

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals with neuroimaging; n=number of affected individuals; WML=white matter lesions(s); PVS=perivascular space(s);

Table S3. Variant Effect Predictor Output Summary

Number of variants							% variants with info	% pathogenic* among variants with data	% pathogenic* among all variants
VARIANT IMPACT/CLASSIFICATION OF SEVERITY (SNPEff)									
	no info	low	moderate*	high*					
HTRA1	7	0	35	11			87%	100%	87%
ADA2	43	3	24	18			51%	93%	48%
COL4A1	43	0	88	23			72%	100%	72%
COL4A2	1	0	14	1			94%	100%	94%
TREX1	21	0	2	8			32%	100%	32%
CTSA	1	0	0	0			0%	0%	0%
Total	116	3	163	61			66%	99%	65%
CLINICAL SIGNIFICANCE (ClinVar)									
	no info	uncertain clinical significance	benign	likely benign	likely pathogenic*	pathogenic*			
HTRA1	30	3	0	0	5	15	43%	87%	38%
ADA2	76	2	1	0	6	3	14%	75%	10%
COL4A1	150	1	0	0	0	3	3%	75%	2%
COL4A2	5	0	0	3	3	5	69%	73%	50%
TREX1	29	0	0	0	1	1	6%	100%	6%
CTSA	1	0	0	0	0	0	0%	0%	0%
Total	291	6	1	3	15	27	15%	81%	12%
IMPACT ON PROTEIN FUNCTION (SIFT)									
	no info	tolerated	deleterious*						
HTRA1	18	1	34				66%	97%	64%

ADA2	43	4	41				51%	91%	47%
COL4A1	46	9	99				70%	92%	64%
COL4A2	1	2	13				94%	87%	81%
TREX1	29	1	1				6%	50%	3%
CTSA	1	0	0				0%	0%	0%
Total	138	17	188				60%	92%	55%
IMPACT ON PROTEIN STRUCTURE AND FUNCTION (PolyPhen-2)									
	no info	benign	possibly damaging*	probably damaging*					
HTRA1	18	0	4	31			66%	100%	66%
ADA2	43	5	1	39			51%	89%	45%
COL4A1	40	2	15	97			74%	98%	73%
COL4A2	1	0	4	11			94%	100%	94%
TREX1	29	2	0	0			6%	0%	0%
CTSA	1	0	0	0			0%	0%	0%
Total	132	9	24	178			62%	96%	59%

*category considered to provide supporting evidence for pathogenicity; SnpEff classifies each variant in one of the following output categories: high impact (variant is assumed to have a disruptive impact in the protein, probably causing protein truncation, loss of function or triggering nonsense mediated decay), moderate impact (non-disruptive variant that might change protein effectiveness), and low impact (variant assumed to be mostly harmless or unlikely to change protein behaviour). The 'modifier' category is taken to represent no information about these categories; ClinVar assigns each variant as pathogenic, likely pathogenic, likely benign, benign, or of uncertain clinical significance; SIFT predicts whether an amino acid substitution is likely to affect protein function based on sequence homology and the physico-chemical similarity between the alternate amino acids, concluding with a qualitative prediction if a variant is deleterious or tolerated; PolyPhen-2 predicts the effect of an amino acid substitution on the structure and function of a protein using sequence homology, 3D structures where available, and a number of other databases and tools. It classifies each variant as probably damaging, possibly damaging or benign.

TABLE S4. Variant Effect Predictor outputs per

gene A. *HTRA1*

Genetic mutation	Protein change	Variant information
c.589C>T	p.R197X	Stop gained, likely deleterious, high impact. Pathogenic
c.865C>T	p.Q289X	Stop gained, likely deleterious, high impact. Pathogenic
c.1108C>T	p.R370X	Stop gained, high impact variant. Pathogenic/likely pathogenic
c.904C>T	p.R302X	Stop gained, high impact variant. Likely pathogenic
c.502A.T	p.K168ter	Stop gained, high impact variant
c.847G>T	p.G283Ter	Stop gained, high impact variant
c.983C>A	p.S328*	Stop gained, high impact variant
c.1005+1G>T		Splice donor variant, high impact
c.971A>C	p.N324T	Missense variant, possible splice region variant with moderate impact. Probably damaging to protein structure and conflicting evidence of tolerated/deleterious to protein function. Likely pathogenic
c.754G>A	p.A252T	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Pathogenic
c.956C>T	p.T319I	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.451C>A	p.Q151K	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinial significance
c.359G>A	p.G120D	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic
c.361A>C	p.S121R	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.397C>G	p.R133G	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Possibly damaging to protein structure but tolerated by protein function
c.367G>T	p.A123S	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Only possibly damaging to protein structure and likely to have deleterious effect on protein function
c.821G>A	p.R274Q	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious/some reports of tolerated to protein function. Pathogenic
c.496C>T	p.R166C	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.517G>A	p.A173T	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.517G>C	p.A173P	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.856T>G	p.F286V	Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function
c.854C>A	p.P285Q	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic
c.854C>T	p.P285L	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic
c.616G>A	p.G206R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance
c.961G>A	p.A321T	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance
c.1091T>C	p.L364P	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.497G>T	p.R166L	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.614C>G	p.S205C	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic

c.852C>A	p.S284R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.883G>A	p.G295R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.889G>A	p.V297M	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.536T>A	p.I179N	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Likely pathogenic
c.827G>C	p.G276A	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Likely pathogenic
c.1021G>A	p.G341J	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.
c.524T>A	p. V175E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.527T>C	p.V176A	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.646 G>A	p.V216 M	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.847G>A	p.G283R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.848G>A	p.G283E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.850A>G	p.S284G	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.905G>A	p.R302Q	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1348G>C	p.D450H	Missense variant with moderate impact. Only possibly damaging to protein structure and deleterious to protein function.

c.184-185del		Intronic variant, with possible impact on both upstream and downsteam gene regulation, ARMS2. Possible influence on lncRNA.
c.830_831delAG	p.E277Vfs	Intronic variant with possible influence on upstream gene
c.126delG	p.E42fs	Frameshift variant with high impact. Pathogenic
c.543delT	p.A182Pfs*33	Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic
c.739delG	p.E247Rfs	Frameshift mutation with high impact. Potentially leading to premature stop
c.958G>A	p.D320N	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.

B. *ADA2*

Genetic mutation	**Protein change**	**Variant information**
c.982G>A	p.E328K	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene, and CTCF binding site. Probably damaging/benign to protein structure and likely deleterious to protein function/potentially tolerated.
c.138/144delG		5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay
c.37_39del	p.K13del	5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay
c.143_144insG	p.R49Afs*13	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144 dup	p.R49Afs*13	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144_145ins		Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144del	p.R49Gfs*4	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic

c.144delG	p.R49fs	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.144dupG	p.R49fs	Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic
c.629delT		Frameshift variant, high impact with potential impact on both upstream and downstream genes.
c.427del	p.I143Sfs*41	Frameshift variant, high impact. Impact on nonsense mediated decay transcript processing. Possible impact on downstream genes
c.1447_1451del	p.S483Pfs*5	Intronic variant, possible impact on transcript processing
c.680- 681delAT		Intronic variant, possible impact on transcript processing
c.973-?_1081+?del	p.V325Tfs*7	Intronic variant, possible retained intron. Could have impact on both upstream, downstream genes and nonsense medicated decay transcript processing.
c.972+3A>G		Intronic, splice region variant with low impact. Possible retained intron and impact on nonsense mediated decay transcript processing
c.326C>A	p.A109D	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.336C>A	p.H112Q	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.336C>G	p.H112Q	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.336G>C	p.H112Q	Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function.
c.962G>A	p.G321E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.133C>T	p.A45T	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.
c.1358A>G	p.Y453C	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.
c.385A>C	p.T129P	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.

c.932T>G	p.L311R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic.
c.1352T>G	p.L451W	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1353G>T	p.L451F	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1360G>C		Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1373T>A	p.V458D	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1223G>A	p.C408Y	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1348G>T	p.G450C	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1367A>G	p.Y456C	Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.Pathogenic
c.1065C>A	p.F355L	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Benign protein structure and tolerated by protein function.
c.1052T>A	p.L351Q	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.

c.1057T>C	p.Y353H	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.1069G>A	p.A357T	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.1072G>A	p.G358R	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.1078A>G	p.T360A	Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function.
c.140G>C	p.G47A	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.278T>C	p.I93T	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.506C>T	p.R169Q	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.506G>A	R169Q	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.533T>C	p.F178S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible retained intron.
c.139G>T	p.G47W	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation, possible impact on processing of pseudogene (FAM32BP). Probably damaging to protein structure and likely to have deleterious effect on protein function.Pathogenic
c.563T>C	p.L188P	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.578C>T	p.P193L	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.139G>A	p.G47R	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting evidence on clinical significance
c.650T>A	p.V217D	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.712G>A	p.D238N	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.872C>T	p.S291L	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.620T>C		Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinical significance
c.791G>C	p.W264S	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging/benign to protein structure and could have deleterious/tolerated impact on protein function. May cause retained intron.
c.1110C>A	p.N370K	Missense variant, moderate impact, possible 3'UTR variant involved in nonsense mediated decay. Probably damaging to protein structure and likely to have deleterious effect on protein function.
c.1445A>G		Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.1226C>A		Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function.
c.752C>T	p.P251L	Missense variant, splice region variant with moderate impact. Possibly damaging to protein structure and tolerated by protein function.
c.424G>A	p.G142S	Missense variant. Change tolerated by protein function, benign impact on protein structure

c.25C>T	p.R9W	Missense variant. Deleterious (but some evidnec of low confidence in finding) to protein function, benign impact on protein structure
c.2T>C	p.M1T	Missense variant. Deleterious (but some evidnec of low confidence in finding) to protein function, benign impact on protein structure
c.73G>T	p.G25C	Missense, splice region variant. Change tolerated by protein function and has benign impact on protein structure
c.882 -2A>G		Splice acceptor variant, high impact . Also potential impact on upstream gene regulation
c.973 -1G>A		Splice acceptor variant, high impact . Also potential regulatory region variant altering TF binding site. Could impact upstream gene regulation (RPL32P5)
c.973 -2A>G		Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay . Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5)
c.973-2A>G		Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay . Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5).
c.542+1G>A		Splice donor variant with high impact. Possible impact on nonsense mediated decay
c.753+2T>A		Splice donor variant with high impact. Possible retained intron
c.753G>A		Splice region variant with low impact. May influence downstream and upstream gene regulation.
c.781delinsCCATA	p.D261Pfs*2	Stop gained, frameshift variant with high impact
c.1196G>A	p.W399*	Stop gained, high impact
c.794C>G	p.Q265X	Stop gained, high impact variant. Possible impact on upstream gene regulation
c.916C>T	p.R306*	Stop gained, high impact variant. Possible impact on upstream gene regulation.
c.660C>A	p.Y220X	Stop gained, high impact variant. Possible impact on upstream gene regulation. Benign.
c.47+2T>C		Synonymous, intron variant with low impact. Potential retained intron

C. *COL4A1*

Genetic mutation	**Protein change**	**Variant information**
c.*35C>A		3' UTR variant, regulatory region variant
c.*31G>T		3'UTR variant, regulatory region variant

c.*32G>A		3'UTR variant, regulatory region variant
c.*32G>T		3'UTR variant, regulatory region variant
c.*33T>A		3'UTR variant, regulatory region variant
c.-2C>T		5'UTR variant, with possible impact on upstream gene regulation
c.2545G>T	p.G808V	Evidence of stop gained, high impact
c.2424delT	p.P810fs	Frameshift mutation with high impact. Potentially leading to premature stop
c.2931dupT	p.G978WfsX15	Frameshift mutation with high impact. Potentially leading to premature stop
c.3702delC	p. G1236*	Frameshift mutation with high impact. Potentially leading to premature stop
c.2085del	p.G696fs	Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic.
c.1121-18G>A		Intronic variant possibly leading to retained intron
c.2645_2646delinsAA	p.G882E	Intronic variant potentially leading to retained intron
c.3877-30C>A		Intronic variant with possible impact on upstream gene regulation. Intron retained
c.4582 -4586 dupCCCATG ins.		Intronic variant, retained intron. Likely deleterious and probably damaging. Possible impact on upstream gene regulation
c.4642T>G	p.C1548G	Missense & splice region variant with low to moderate effect. Likely to impact protein function and probably damaging
c.2969G>A	p.G990E	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.2969G>T	p.G990V	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.3200G>A	p. G1067E	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.3200G>C	p.G1067A	Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging.
c.3770G>C	p.G1257E	Missense variant in possible regulatory region. Likely deleterious and probably damaging
c.3796G>C	p.G1266R	Missense variant in possible regulatory region. Likely deleterious and probably damaging
c.3832G>T	p.G1278S	Missense variant in possible regulatory region. Likely deleterious and probably damaging. Uncertain clinical significance

c.3245G>A	p.G1082E	Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging
c.3280G>C	p.G1094R	Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging
c.1249G>C	p.G417R	Missense variant with moderate impact. Benign impact on protein structure and deleterious to protein function
c.3997G>A	p.D1333N	Missense variant with moderate impact. Conflicting evidence of effect on protein function, potentially tolerated/potentially deleterious
c.3592G>A	p.G1198R	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3620G>T	p.G1207V	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3656G>A	p. G1219E	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3671C>T	p.P1224L	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3704A>G	p.K1235R	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3706G>A	p.G1236R	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3707G>A	p. G1237E	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3712C>T	p.R1238C	Missense variant with moderate impact. Likely deleterious and probably damaging
c.3505G>A	p. G1169S	Missense variant with moderate impact. Possible splice region variant, with potential impact on downstream gene regulation. Likely deleterious and probably damaging
c.2512A>G	p.M838V	Missense variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.3389G>A	p.G1130D	Missense variant with moderate impact. Potentially modifies upstream and downstream gene regulation. Likely deleterious and probably damaging
c.4088 G > A	p.G1363D	Missense variant with moderate impact. Probably damaging and deleterious to protein function
c.1502G>A		Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1528G>A	p.G510R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1583G>A	p.G528E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function

c.1619A>G	p.K540R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2008G>A	p.G670R	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2045G>T	p. G682V	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2063G>A	p.G688D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2078G>A	p.G693E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2086G>A	p.G696S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2086G>T	p.G696C	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2132G>A	p.G711E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2159G>A	p.G720D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2168G>A	p. G723E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2504G>A	p.G835E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.625G>A	p. G209S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.634G>A	p.G212S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.1493G>A	p.G498D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic.

c.1493G>T	p.G498V	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic.
c.3383T>A	p.I1128N	Missense variant with moderate impact. Substitution seems to be tolerated by protein function but probably damaging to protein structure
c.3715G>A	p.G1239R	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.3941G>T	p.G1314V	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.3976G>A	p.G1326R	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.3995G>A	p.G1332D	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.4031G>C	p.G1344A	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.4105G>C	p.G1369R	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.4213G>A	p.G1405S	Missense variant with possible impact on upstream gene regulation. Probably damaging variant
c.1801G>A	p. G601S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function
c.1807C>T	p.P603S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function
c.1555G>A	p.G519R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1835G>A	p.G612D	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1853G > A	p.G618E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2494G>A	p.G832R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2563G>C	p.G855R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2581G>A	p.G861S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2599G>A	p.G867R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.2608G>A	p.G870R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2636G>A	p.G879E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2645G>A	p.G882D	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2662G>A	p.G888R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2689G>A	p.G897S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2699G>A	p.G900E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2744G>A	p.G915E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2782G>C	p.D928H	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2842G>A	p.G948S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2987G>A	p.G996D	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3022G>A	p.G1008R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3040G>C	p.G1014R	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3104G>T	p.G1035V	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3122G>A	p.G1041E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.3130G>C	p.G1044E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.3190G>A	p.G1064S	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.191G>T	p.G64V	Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible 3'UTR variant.
c.4739G>C	p.G1580A	Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging
c.4881C>G	p.N1627K	Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging
c.4843G>A	p.E1615K	Missense variant, Moderate impact, possibly retained intron, probably damaging
c.4232G>C	p.G1411A	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4380T>G	p.C1460W	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4652G>A	p. C1551Y	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4717G>A	p.G1573R	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4738 G > A	p.G1580S	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.4738G>A	p. G1580S	Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function
c.1955G>A	p. G652E	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1963G>A	p.G655R	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function

c.1964G>A	p.G655E	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1973C>A	p. G658V	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.1973G>A	p.G658D	Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function
c.2441 G > T	p.G814V	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.2413G>A	p.G805R	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.2413G>C	p. G805R	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function
c.2317G>A	p.G773R	Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2317G>C	p.G773R	Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2228G>T	p.G743V	Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function
c.2245G>A	p.G749S	Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function
c.2263G>A	p.G755R	Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function
c.4267G>C	p.G1423R	Missense variant, possibly resulting in retained intron. Possibly damaging and likely deleterious to protein function
c.4133G>A	p.G1378D	Missense variant, potentially impacting upstream gene regulation. Likely deleterious and probably damaging

c.4150+1(IVS46) G>T		Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious.
c.4150+1G>A		Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious.
c.4150G>A	p.G1384S	Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious.
c.2345G>C	p.G782A	Missense variant, splice region variant with low-moderate impact. Likely deleterious and probably damaging
c.2096G>A	pG699D	Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure
c.236G>T	p.G79V	Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure
c.443G>A	p.G148E	Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure
c.196C>A	p.Q66K	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.2641A>G	p.M881V	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.3046A>G	p.M1016V	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.31C>A	p.L11M	Missense variant. Change tolerated by protein function but possibly damaging to protein structure
c.1612C>G	p.R538G	Missense variant. Change tolerated by protein function with benign impact on protein structure
c.1769G>A	p.G562E	Missense variant. Change tolerated by protein function with benign impact on protein structure
c.3946C>G	p.Q1316E	Missense variant. Change tolerated by protein function, likely benign some evidence of possibly damaging protein structure
c.1537-2A>G		Potential frameshift variant and splice acceptor variant with high impact
c.1537–2delA		Potential frameshift variant and splice acceptor variant with high impact
c.1121-2dupA	p.G374_N429 delinsD	Splice acceptor variant, intronic variant leading to retained intron. High impact variant.
c.1382-1G>C		Splice acceptor variant, intronic variant leading to retained intron. High impact variant.
c.2194-1G.A		Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure

c.553-2A>G		Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure and altered downstream gene regulation. Potential 3' UTR variant
c.1990+1G>A		Splice donor variant with high impact. Possible retained intron
c.3406 + 1G>T		Splice donor variant with high impact. Potential impact on both upstream and downstream gene regulation
c.2716 + 1G>A		Splice donor variant with high impact. Potential impact on downstream gene regulation
c.2716+ G>T		Splice donor variant with high impact. Potential impact on downstream gene regulation
c.2716+2T>C		Splice donor variant with high impact. Potential impact on downstream gene regulation
c.2458+1G>A		Splice donor variant, high impact. Possibly retained intron and downstream gene regulation modification
c.1A>T		Start lost, but seems to be tolerated by protein function but possibly damaging to protein structure. Possible impact on upstream gene regulation
c.739C>T	p.Q247*	Stop gained, high impact. Possible modifier of downstream gene regulation
c.607G>T	p. G203R	Stop gained, high impact. Potential 3'UTR regulatory variant
c.4875C>A	p.Y1625*	Stop gained, likely deleterious, high impact
c.4887C>A	p.Y1629X	Stop gained, likely deleterious, high impact
c.1870G>T	p.G624*	Stop gained, likely deleterious, high impact. Possible modifier of downstream gene regulation

D. *COL4A2*

Genetic mutation	**Protein change**	**Variant information**
c.1396G>A	p.G466S	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Possible intron variant causing alteration to lncRNA influencing gene AS2
c.1776+1G>A		Splice donor variant with high impact. Possible retained intron and impact to lncRNA influencing gene AS2. Pathogenic but also reported to have uncertain clinical significance
c.1810G>C	p.G604R	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potenital influence on promoter refulation and lncRNA influencing AS2

c.1856G>A	p.G619D	Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potenital influence on promoter refulation and lncRNA influencing AS2. Likely pathogenic
c.2105G>A	p.G702D	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function
c.2399G>A	p.G800E	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. With possible impact on upstream gene regulation and promoter regions
c.2821G>A	p.G941R	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Possible retained intron.
c.3110G>A	p.G1037E	Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic
c.3368A>G	p.E1123G	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Likely benign clinical significance but possible risk factor
c.3448C>A	p.Q1150K	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and tolerated to protein function. Likely benign clinical significance but possible risk factor
c.3455G>A	p.G1152D	Missense variant, splice region variant. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.3490G>A	p.R1164G	Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic
c.4129G > A	p.G1377R	Missense variant, moderate impact and potential modifier of upstream gene regulation, possible impact on lncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic
c.4147G>A	p.G1383R	Missense variant, moderate impact and potential modifier of upstream gene regulation, possible impact on lncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic
c.4987G>A	p.G1663S	Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation, possible impact on lncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting clinical significane, reported both likely benign and likely pathogenic
c.5068G>A	p.A1690T	Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and tolerated to protein function. Likely benign clinical significance but possible risk factor

E. *TREX1*

Genetic mutation	Protein change	Variant information
c.703dup	p.V235GfsX6	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.822delT	p.P275Qfsx2	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.830-833dupAGGA	p.D278fs	Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5
c.829A>T	p.K277*	Stop gained, high impact. Possible modifier of downstream gene regulation. Likely pathogenic.
c.828_831dupGAAG	p.D278EfsTer48	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.703dupG	p.V235Gfs	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.685A>G	p.Arg229Gly	Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and tolerated by protein function
c.690G>T	p.Lys230Asn	Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and could have deleterious effect on protein function, but tolerated also reported
c.581delC	p.Ala194fs	Frameshift variant with high impact, possible downstream gene regulation of ATRIP and SHISA5. Pathogenic
c.742_745dupGTCA	p.T249fs	Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5
c.734dupC	?	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)
c.911_912delCA	p.T304Nfs*12	Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5
c.703_704insG	p.V235GfsX6	Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay)

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