SUPPLEMENTAL MATERIAL

Contents

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

Supplemental Results

Table I. Frequency and Subtypes of Cerebral Clinical Features

		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 II. 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 III. 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 IV. Variant Effect Predictor outputs per gene

Table IV 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.

Table IV 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

Table IV 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

Table IV 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

Table IV 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)

Appendix I. 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

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