

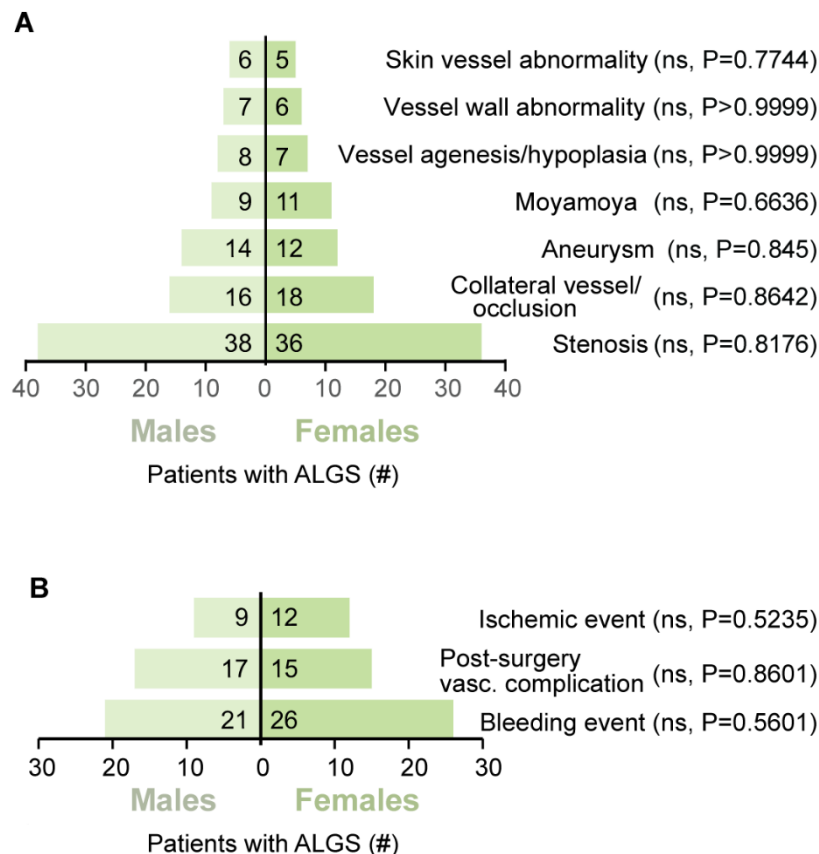
EMM-2022-15809 Appendix

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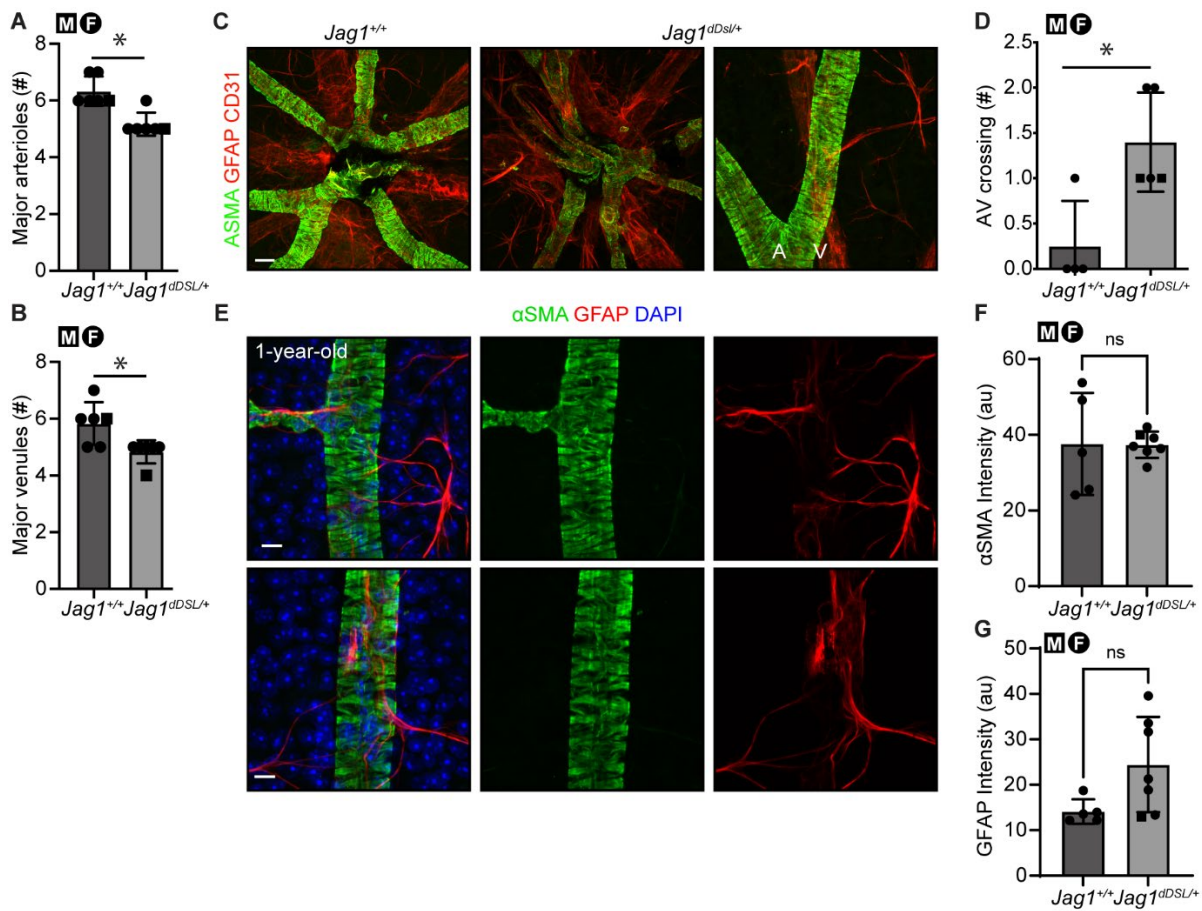
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Appendix Figure S1



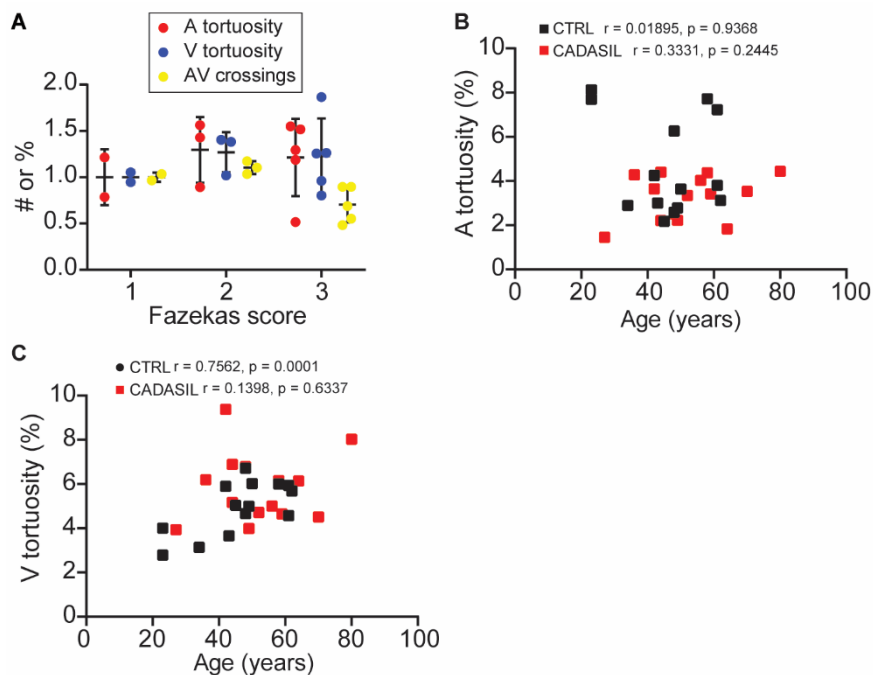
Appendix Figure S1. Summary of most common events identified in Systematic Review, with ALGS, vascular anomalies or bleeding and sex data reported. (A) Structural vascular abnormalities grouped by prevalence in male or female patients with ALGS. Differences between males and females are not significant (Binomial exact test of observed vs expected 50%/50%, two-sided for conditions $n \geq 5$. Overall number male vs females: 95 vs 81 ns $P=0.3271$. Skin vessel abnormalities $P=0.7744$, vessel wall abnormalities $P=>0.9999$, vessel agenesis/hypoplasia $P>0.9999$, Moyamoya $P=0.5235$, Aneurysms $P>0.9999$, Collateral vessels occlusions $P=0.8679$, Stenoses $P=0.8199$. Please note that vascular bruits may include pulmonary stenosis, and Moyamoya includes stenosis and collateral vessels. (B) Functional vascular abnormalities grouped by prevalence in male or female patients with ALGS. All differences not significant. (Binomial exact test of observed vs expected 50%/50%, two-sided for conditions $n \geq 5$. Ischemic events $p=0.8388$, Surgery-related vascular complications $P=0.8601$, Bleeding events (not including surgery-related) $P=0.8776$). The numbers inside the graph bars in A and B depict the number of individuals reported with a given anomaly per sex. Some patients had multiple vascular events and are included in several categories. For references and full details, see also Source data for Figure 1.

Appendix Figure S2



Appendix Fig S2. *Jag1*^{ADsl/+} mice display a mild vascular phenotype. (A,B) Quantification of arterioles (A) and venules (B) in control and *Jag1*^{ADsl/+} mice at 1 year of age (Mann-Whitney test, Arterioles P=0.0108, Venules P=0.0455). (C,D) Staining for α SMA-positive arterioles and GFAP/CD31-positive venules (C), and quantification of artery-vein crossings at all stages investigated (Mann-Whitney test, P=0.0317) (D). (E) Immunofluorescence staining for α SMA and GFAP in 1-year-old control and *Jag1*^{ADsl/+} retinas. (F,G) Quantification of α SMA (Mann-Whitney test, P=0.7551) (D) and GFAP (Mann-Whitney test, P=0.0732) (E) intensity per area. au= arbitrary units.

Appendix Figure S3



Appendix Figure S3. CADASIL vessel tortuosity correlation analyses. (A) Lack of correlation for arteriolar and venous tortuosity and arteriovenous crossing to Fazekas scores for CADASIL and control patients. The data for each parameter are normalized to the average value of each parameter corresponding to Fazekas score 1 value. Analyzed by 2-way ANOVA, Interaction $P=0.3818$, Fazekas score $P=0.4829$, Phenotype $P=0.1373$, $n=10$. (B) Correlation analysis between arterial tortuosity and age for CADASIL and age-matched control patients, $n=14$ per group, analyzed by Pearson r . (C) Correlation analysis between venous tortuosity and age for CADASIL and age matched control patients, $n=14$ per group, analyzed by Pearson r . Each dot represents one individual; graphs depict mean values \pm standard deviation. A, arteriole; AV, arteriovenous; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; V, venule

Appendix Table S1

Appendix Table S1. Systematic literature review. Table describes patients' sex, structural anomaly or functional event. F, female; M, male; MAPCA, major aortopulmonary collateral arteries. Please note that all cases of Moyamoya are also described as having collaterals and stenosis. "Stenosis / coarctation" includes mid-aortic syndrome. Ischemic events include embolism, stroke, thrombosis and inadequate circulation.

Patient number	Sex	Stenosis/ coarctation	Hemorrhages/ bleeding	Hematoma	Ischemic event	Collateral vessel/ occlusion	Moyamoya	Aneurysm	Vessel agenesis / hypoplasia	Vessel wall abnormality	Skin blood vessel abnormalities	Post-surgery complications	Ref	Additional notes
1	F	Y										Y	1	
2	F		Y										2	
3	F		Y										2	
4	F		Y										2	
5	F		Y										2	
6	F		Y										2	
7	F		Y										3	
8	F											Y	4	Nephrotic syndrome 13 years after liver transplant- Arteriolar hyalinosis.
9	F											Y	5	Female died post-surgery due to profound vasodilation, unresponsive to vasopressin, norepinephrine, and oxygen.
10	F	Y			Y	Y	Y						6,7	Baird et al Patient 1 = Emerick et al Patient 25
11	F	Y	Y		Y	Y	Y						7	Baird et al Patient 5
12	F											Y	8	Evans syndrome and arterial thrombosis after liver transplant.
13	F				Y								9	
14	F												10	Persistent falcine sinus.
15	F												10	Developmental venous anomaly.
16	F					Y							11	MAPCAs.
17	F												12	Tortuous vessels in retina and retinopathy.

18	F		Y							Y			13	
19	F				Y								14	Deep vein thrombosis after valvuloplasty for pulmonary stenosis. Normal clotting, treated with anticoagulants.
20	F		Y										6	Emerick et al patient #2
21	F		Y					Y					6	Emerick et al patient #5
22	F							Y					6	Emerick et al patient #6
23	F	Y			Y								6	Emerick et al patient #8
24	F				Y								6	Emerick et al patient #1
25	F										Y		15	
26	F	Y											16	Hypotonia requiring dopamine.
27	F	Y									Y		17	
28	F		Y	Y									18	
29	F								Y				19	
30	F		Y										20	
31	F	Y	Y			Y	Y	Y					21	
32	F										Y		22	
33	F	Y											23	
34	F		Y							Y			24	
35	F	Y											25	Takayashi arteritis
36	F							Y					25	Arteriosclerosis
37	F	Y											26	
38	F	Y			Y	Y	Y						27	Article in Korean, figure legends in English.
39	F	Y			Y	Y	Y	Y			Y		28	Livedo reticularis
40	F		Y										29	
41	F	Y			Y	Y							30	Arteriosclerosis, MAPCAs
42	F					Y							31	MAPCAs.
43	F					Y			Y				32	

68	F											Y	57	Perfusion defects in lungs. Right hemiparesis due to a cerebral thromboembolism during cardiac catheterization.
69	F			Y									58	
70	F	Y											59	
71	F										Y		60	
72	F										Y		60	
73	F	Y				Y			Y				61	
74	F	Y			Y	Y	Y						62	
75	F	Y			Y	Y	Y						62	
76	F											Y	63	
77	F	Y							Y				64	Abdominal aorta with 50% concentric narrowing.
78	F	Y											64	
79	F										Y		65	Double mutant NOTCH2 RASA1, AVM. type II Abernethy malformation in the hepatic portal vein
80	M										Y		66	
81	M		Y										2	
82	M		Y										2	
83	M		Y										2	
84	M		Y										2	
85	M		Y										2	
86	M		Y										2	
87	M		Y										2	
88	M		Y										2	
89	M		Y										2	
90	M	Y											67	
91	M											Y	68	
92	M	Y			Y	Y	Y						69	
93	M	Y			Y	Y	Y						6,7	Baird et al Patient 3 = Emerick et al Patient 20

94	M	Y			Y	Y	Y						6,7	Baird et al Patient 2 = Emerick et al Patient 9
95	M	Y			Y	Y	Y						7	Baird et al Patient 4
96	M		Y					Y					70	
97	M												10	Persistent falcine sinus.
98	M	Y			Y	Y	Y						10	
99	M							Y		Y			10	
100	M							Y		Y			10	
101	M									Y			10	Dolichoectasia
102	M	Y			Y	Y	Y						10	
103	M							Y		Y			10	Persistent falcine sinus
104	M	Y											71	
105	M	Y			Y	Y	Y						72	
106	M	Y	Y					Y					73	
107	M			Y									6	Emerick et al patient 10
108	M										Y		6,74	Emerick et al patient 19 & single patient reported by sex in Emerick et al 1999
109	M	Y			Y				Y				6	Emerick et al patient 21
110	M	Y											6	Emerick et al patient 22
111	M								Y				6	Emerick et al Patient 23
112	M	Y											6	Emerick et al Patient 24
113	M										Y		15	Mid -aortic syndrome Boy in Fig 1
114	M	Y				Y					Y		75	
115	M								Y				76	Two-vessel cord (only one artery in umbilical cord- usually there are two.) Stillborn
116	M										Y		22	

141	M	Y				Y		Y					43	
142	M	Y				Y		Y	Y				43	
143	M	Y											43	
144	M	Y				Y							43	
145	M	Y											44	
146	M	Y											44	
147	M	Y											44	
148	M	Y									Y		44	
149	M										Y		44	
150	M										Y		44	
151	M	Y							Y				45	
152	M		Y										45	
153	M	Y							Y				99	Boy with anomalies as described. Father with renal failure and cerebrovascular complications - died before diagnosis - no liver defects.
154	M	Y						Y			Y		100	
155	M	Y											51	
156	M	Y											51	
157	M					Y							101	Systemic to pulmonary artery collateral vessels but did not resemble a true ductus arteriosus.
158	M							Y					102	
159	M	Y				Y	Y						103	
160	M							Y					56	
161	M							Y					104	
162	M										Y		60	
163	M										Y		60	
164	M										Y		60	
165	M										Y		63	
166	M										Y		63	

167	M											Y	63	
168	M	Y				Y							105	Vascular bruits/turbulent flow.
169	M												64	Fragile renal arteries.
170	M												64	Fragile renal and abdominal arteries.
171	M	Y											106	
172	M	Y							Y				107	NOTCH2 mutation. Filiform endings of peripheral vessels.
Sum Females		36	21	5	12	18	11	12	7	6	5	15		
Sum Males		38	16	5	9	16	9	14	8	7	6	17		

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Appendix Table S2

Appendix Table S2

Measured parameter	P value	Significant difference for sex?	Additional Comments
1B Spontaneous intracranial bleeds (PRISMA review)	0.0117	YES	10 females with bleeds vs 1 male
2A Survival of <i>Jag1^{Ndr/Ndr}</i> mice vs WT, by sex	>0.05	NO	Female <i>Jag1^{Ndr/Ndr}</i> mice die earlier than males and survival at P10 is lower, but the differences are not statistically significant between male and female <i>Jag1^{Ndr/Ndr}</i> mice.
2B Total Bilirubin at P10	Not tested	Not tested	Differences between sexes not suggested by first 6 animals, additional biological replicates not justified.
2C TAT at P10	Not tested	Not tested	Differences between sexes, or between <i>Jag1^{Ndr/Ndr}</i> mice vs WT mice, not supported by first 6 animals, additional biological replicates not justified.
2D Fibrinogen at P10	Not tested	Not tested	Differences between sexes, or between <i>Jag1^{Ndr/Ndr}</i> mice vs WT mice, not supported by first 6 animals, additional biological replicates not justified.
2E INR at P10	Not tested	Not tested	Differences between sexes, or between <i>Jag1^{Ndr/Ndr}</i> mice vs WT mice, not supported by first 6 animals, additional biological replicates not justified.
2F Tail bleeding time at P10	Not tested	Not tested	Differences between sexes, or between <i>Jag1^{Ndr/Ndr}</i> mice vs WT mice, not supported by first 6 animals, additional biological replicates not justified.
2H Skull Full thickness bone volume	>0.05	No interaction of genotype with sex in two-way ANOVA	One outlier <i>Jag1^{Ndr/Ndr}</i> male with very low skull volume: this male was inordinately small compared to other <i>Jag1^{Ndr/Ndr}</i> mice. This is a sporadic phenomenon in the <i>Jag1^{Ndr/Ndr}</i> colony.

2I Skull compact bone volume	>0.05	No interaction of genotype with sex in two-way ANOVA	One outlier <i>Jag1^{Ndr/Ndr}</i> male with very low skull volume: this male was inordinately small compared to other <i>Jag1^{Ndr/Ndr}</i> mice. This is a sporadic phenomenon in the <i>Jag1^{Ndr/Ndr}</i> colony.
2K Resin leakage outside blood vessels in liver casts	>0.05	No interaction of genotype with sex in two-way ANOVA and no difference in t-test of male vs female <i>Jag1^{Ndr/Ndr}</i> mice	All three <i>Jag1^{Ndr/Ndr}</i> females exhibit some vascular weakness/resin leakage, and two of three had very large provoked leakage outside blood vessels. Two of three male <i>Jag1^{Ndr/Ndr}</i> mice had small vascular leakages.
2L Evans Blue in brain	>0.05	No difference in t-test of male vs female <i>Jag1^{Ndr/Ndr}</i> mice	Animal with largest amount of Evans blue in brain (outlier compared to controls) is a male <i>Jag1^{Ndr/Ndr}</i> mouse.
3B Arteriovenous crossings in adult retina	>0.05	No interaction of genotype with sex in two-way ANOVA and no difference in Tukey's multiple comparisons test of male vs female <i>Jag1^{Ndr/Ndr}</i> mice	
3C Number of Major Arterioles in adult retina	>0.05	No interaction of genotype with sex in two-way ANOVA and no difference in Tukey's multiple comparisons test of male vs female <i>Jag1^{Ndr/Ndr}</i> mice	
3D Number of Major venules in adult retina	0.0302	Interaction of genotype with sex in two-way ANOVA ($p=0,044$) and difference in Tukey's multiple comparisons test of male vs female	Sex-specific venous defect: Adult <i>Jag1^{Ndr/Ndr}</i> females have significantly fewer major venules in retina than males

		Jag1Ndr/Ndr mice (p=0,0302)	
3E Arterial Tortuosity by stage	Not tested	Not tested	
3F Arterial Tortuosity by sex	>0.05	No interaction of genotype with sex in two-way ANOVA and no difference in Tukey's multiple comparisons test of male vs female Jag1Ndr/Ndr mice	
3G Venous Tortuosity by stage	Not tested	Not tested	
3H Venous Tortuosity by sex	0.0031	Interaction of genotype with sex in two-way ANOVA (p= 0,0223) and difference in Tukey's multiple comparisons test of male vs female Jag1Ndr/Ndr mice (p=0,0031)	Sex-specific venous defect: Adult <i>Jag1^{Ndr/Ndr}</i> females have significantly higher venous tortuosity in retina than males
3J Middle Cerebral Artery Tortuosity at P10	>0.05	No interaction of genotype with sex in two-way ANOVA	
3L Middle Cerebral Artery Branching at P10	>0.05	No interaction of genotype with sex in two-way ANOVA	
4F aSMA gaps per age group	Not tested	Not tested	1 out of 3 of adult <i>Jag1^{Ndr/Ndr}</i> show aSMA gaps in retina, increased to 3 out of 6 mice in 1-year-old <i>Jag1^{Ndr/Ndr}</i> age group (all males)
4G aSMA negative gaps per retina	Not tested	Not tested	1-year-old <i>Jag1^{Ndr/Ndr}</i> mice (N=6) had significantly more aSMA gaps in retina compared to 1-year-old WT (of which the three males had the highest increase)

4J Cleaved Caspase 3+ cells	Not tested	Not tested	Significantly more apoptotic cells in 1-year-old <i>Jag1^{Ndr/Ndr}</i> mice compared to 1-year-old WT (the three males had the highest increase)
4L Middle Cerebral Artery aSMA nuclei	Not tested	Not tested	
4N Mean Blood pressure	>0.05	No interaction of genotype with sex in two-way ANOVA	
4O Systolic Blood pressure	Not tested	Not tested	
4P Evans Blue-Angiotensin II in adult brain	Not tested	Not tested	
4S aSMA negative gaps Angiotensin II	Not tested	Not tested	
5B SCP Branching Points P30	Not tested	Not tested	
5C ICP Vascular Length P30	Not tested	Not tested	
5D ICP Branching Points P30	Not tested	Not tested	
5F SCP Branching Points 3-6 months	Not tested	Not tested	
5G ICP Vascular Length 3-6 months	Not tested	Not tested	
5H ICP Branching Points 3-6 months	Not tested	Not tested	
5J Collagen IV sleeve 3-6 months	Not tested	Not tested	Empty COLIV sleeves per are increased in ICP of two <i>Jag1^{Ndr/Ndr}</i> females
5L Vertical sprouts 3-6 months	Not tested	Not tested	
5M Vertical Sprouts 1 year	Not tested	Not tested	
5P Neurofilament coverage	Not tested	Not tested	
6B CADASIL AV Crossings	Not tested	Not tested	
6C CADASIL Number of Major Arterioles in retina	Not tested	Not tested	
6D CADASIL Number of Major Venules in retina	Not tested	Not tested	
6E CADASIL Arterial Tortuosity	Not tested	Not tested	
6F CADASIL Venous Tortuosity	Not tested	Not tested	

6G ALGS AV Crossings	Not tested	Not tested	
6H ALGS Number of Major Arterioles in retina	Not tested	Not tested	
6I ALGS Number of Major Venules in retina	Not tested	Not tested	
6J ALGS Arterial Tortuosity	Not tested	Not tested	
6K ALGS Venous Tortuosity	Not tested	Not tested	

Appendix Supplementary Materials and Methods

Systematic review search strategy

The Medline (Ovid), Embase and Web of Science Core Collection database were used for publication search. After the initial search, automated deduplication was performed by the Karolinska Institutet library. The databases were searched up to June 14th, 2021. Two reviewers manually screened, reviewed and collected each record independently. The systematic review followed the Prisma 2000 guidelines (25). The systematic review was not registered, and a review protocol was not prepared. Records that had no abstract available in English and publications that were not accessible were excluded. Publications that were included in the systematic review contained information about the ALGS diagnosis, patient sex and vascular events except for pulmonary artery stenosis, which is a hallmark of ALGS. Patients that explicitly did not meet the criteria for diagnosis (genetically confirmed, or presenting three of five diagnostic features, or relatives of confirmed cases with at least two hallmarks) were excluded. Additional reasons for exclusion were bleeding as a consequence of hepatocellular carcinoma, displaced blood vessels secondary to other primary defects, splenic hamartoma (benign splenic mass, not thought of as a vascular lesion), or aortic stenosis stated to be a consequence of a bicuspid valve. Assumption was made about the patient's sex if the patient was referred to as "he" (male) and "she" (female). Non-peer reviewed abstracts from conferences were included. Structural abnormalities and vascular events were tabulated for all reports. Structural abnormalities quantified included stenosis, collateral vessel or occlusion, aneurysm, Moyamoya, vessel agenesis or hypoplasia, vessel wall abnormality, skin vessel abnormality, vascular bruits and persistent falcine sinus. Vascular events included ischemic or hemorrhagic events or post-surgical vascular complications. The findings of the studies were tabulated and compared for males and females. If a study contained a vascular abnormality that was not part of any group of the synthesis, the patient's information was included only in the patient overview table (Table S1). After the full screen by two reviewers, the two independent

lists were compared and discussed to identify any mismatches and determine final inclusion/exclusion. Articles with relevant vascular information but lacking sex data were pursued by contacting study authors for more information. None of the study authors were able to provide sex data where this was missing from the original publication. One potential source of bias in the reports included is presented by the fact that the majority come from hepatology centers, which follow the patients for liver involvement and may therefore exhibit publication bias towards more overt vascular events such as intracranial hemorrhage. Therefore, different types of bleeding events (eg nose bleeds versus intracranial bleeds) should not be compared with one another. There is no obvious risk of bias comparing impact of sex within each vascular event. To help reduce publication bias from double reporting we describe the total number of assessed publications as “Reports included in studies” and the total number of assessed publication per patient as “Studies included in review”. Data are presented as summary of reported events in males and females and the difference between males and females was tested using two-tailed binominal exact test. For observed vs expected outcomes, a 1:1 distribution of cases between males and females was assumed to be expected.

Search strategy for Medline:

Field labels: exp/ = exploded MeSH term; / = non exploded MeSH term; .ti,ab,kf. = title, abstract and author keywords; adjx = within x words, regardless of order; * = truncation of word for alternate endings

1. Alagille Syndrome/
2. (alagill* adj3 (syndrome* or watson or disease)).ti,ab,kf.
3. (watson miller or arteriohepatic dysplasia or cardiovertebral syndrome or hepatic ductular hypoplasia or hepatofacioneurocardiovertebral or cholestasis with peripheral pulmonary stenosis or paucity of interlobular bile ducts or hepatic ductular hypoplasia).ti,ab,kf. or/1-3
5. exp Cardiovascular System/ab, pa [Abnormalities, Pathology]
6. exp Vascular Diseases/
7. exp Hemorrhage/
8. exp Vascular Malformations/
9. (vascula* or cerebrovasc* or stroke* or aneurysm* or blood vessel* or artery or arteries or vein* or venous or moyamoya or moya moya or bleed* or hemorrhag*).ti,ab,kf.
10. or/5-9
11. 4 and 10
12. remove duplicates from 11

Search strategy for Embase:

Field labels: /exp = exploded Emtree term; /de = non exploded Emtree term; ti,ab = title and abstract; NEAR/x = within x words, regardless of order; * = truncation of word for alternate endings ((alagille syndrome'/de) OR ((alagill* NEAR/3 (syndrome* OR watson OR disease)):ti,ab,kw) OR ('watson miller':ti,ab,kw OR 'arteriohepatic dysplasia':ti,ab,kw OR 'cardiovertebral syndrome':ti,ab,kw OR hepatofacioneurocardiovertebral:ti,ab,kw OR 'cholestasis with peripheral pulmonary stenosis':ti,ab,kw OR 'paucity of interlobular bile ducts':ti,ab,kw OR 'hepatic ductular hypoplasia':ti,ab,kw)) AND (('cardiovascular system'/exp AND (abnormal* OR patholog*)) OR ('vascular disease'/exp) OR ('bleeding'/exp) OR (vascula*:ti,ab,kw OR cerebrovasc*:ti,ab,kw OR stroke*:ti,ab,kw OR aneurysm*:ti,ab,kw OR 'blood vessel*':ti,ab,kw OR artery:ti,ab,kw OR arteries:ti,ab,kw OR vein*:ti,ab,kw OR venous:ti,ab,kw OR moyamoya:ti,ab,kw OR 'moya moya':ti,ab,kw OR bleed*:ti,ab,kw OR hemorrhag*:ti,ab,kw))

Search strategy for Web of Science Core Collection:

Field labels: TS/Topic = title, abstract, author keywords and Keywords Plus; NEAR/x = within x words, regardless of order; * = truncation of word for alternate endings TS=(alagill* NEAR/3 (syndrome* OR watson OR disease)) OR TS=("watson miller" OR "arteriohepatic dysplasia" OR "cardiovertebral syndrome" OR hepatofacioneurocardiovertebral OR "cholestasis with peripheral pulmonary stenosis" OR "paucity of interlobular bile ducts" OR "hepatic ductular hypoplasia") AND TS=(vascula* OR cerebrovasc* OR stroke* OR aneurysm* OR "blood vessel*" OR artery OR arteries OR vein* OR venous OR moyamoya OR "moya moya" OR bleed* OR hemorrhag*)

Prisma 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Materials and Methods, Introduction, Results
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction & Results
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Appendix Materials and Methods
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.	Appendix Materials and Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix Materials and Methods
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.	Appendix Materials and Methods
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.	Appendix Materials and Methods
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.	Appendix Materials and Methods Figure 1 Source Data, Hankeova et al Systematic Review Table Included Reports
	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.	Appendix Materials and Methods

Section and Topic	Item #	Checklist item	Location where item is reported
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.	Appendix Materials and Methods
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.	Appendix Materials and Methods, Figure 1B, Appendix Figure S1
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)).	Appendix Materials and Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Appendix Materials and Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Appendix Materials and Methods, Figure 1 Source Data
	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.	Appendix Materials and Methods, Figure 1 Source Data
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
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.	Appendix Materials and Methods, Flow Diagram at the end of this Appendix
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Appendix Table S1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix Materials and Methods

Section and Topic	Item #	Checklist item	Location where item is reported
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.	Figure 1, Figure S1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	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.	Figure 1, Source data for Figure 1
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Results section
	23b	Discuss any limitations of the evidence included in the review.	Results section
	23c	Discuss any limitations of the review processes used.	Results section
	23d	Discuss implications of the results for practice, policy, and future research.	Results section
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.	Appendix Materials and Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Appendix Materials and Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements and Funding section
Competing interests	26	Declare any competing interests of review authors.	Conflict of interest statement
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.	Table 1, Table S1

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/>

Prisma 2020 Flow Diagram

