Université de Paris

Centre Ophtalmologique de l'Odéon, Paris

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

TORTUOSITÉS ARTÉRIELLES DOMINANTES

Valérie Krivosic, Alain Gaudric

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

cervco
CENTRE DE RÉFÉRENCE DES MALADIES VASCULAIRES RARES DU CERVEAU ET DE L'ŒIL

Tortuosité artérielle rétinienne familiale

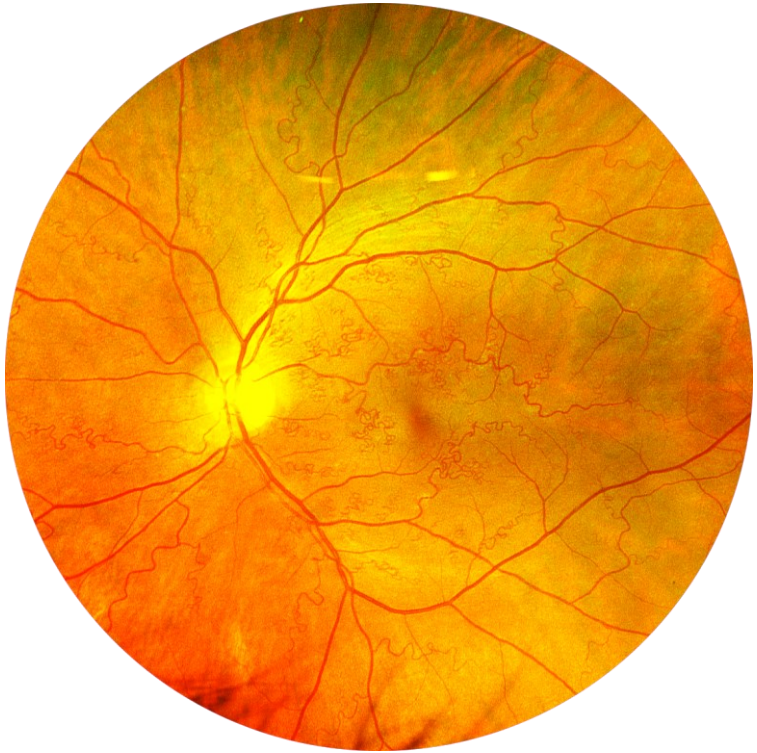
- Première publication en 1958
- *Beyer EM Familiare tortuositas der kleinen netzhautarterien mit makulablutung. Klin Monatsbl Augenheilkd. 1958*

- Un peu plus de 100 cas décrits dans la littérature
- *Familial Retinal Arteriolar Tortuosity: A Review, F. Sutter, Survey of ophthalmology 2003*
- 16 familles, 13 cas sporadiques
- Autosomique dominant

- Initialement décrit comme une anomalie rétinienne isolée

Introduction

- Diagnosis of fRAT is based on clinical findings of bilateral increase tortuosity of small and medium-sized arterioles in the peripapillary and macular regions.
- Corkscrew and spiral vessels may occur, but microaneurysms, arteriovenous shunts and other perivascular abnormalities are uncommon
- Fluorescein angiography highlight the vascular tortuosity and rule out the presence of leakage, staining or hypoperfusion
- OCTA confirmed that only the arterioles are involved
- Positive family history, autosomic dominant inheritance

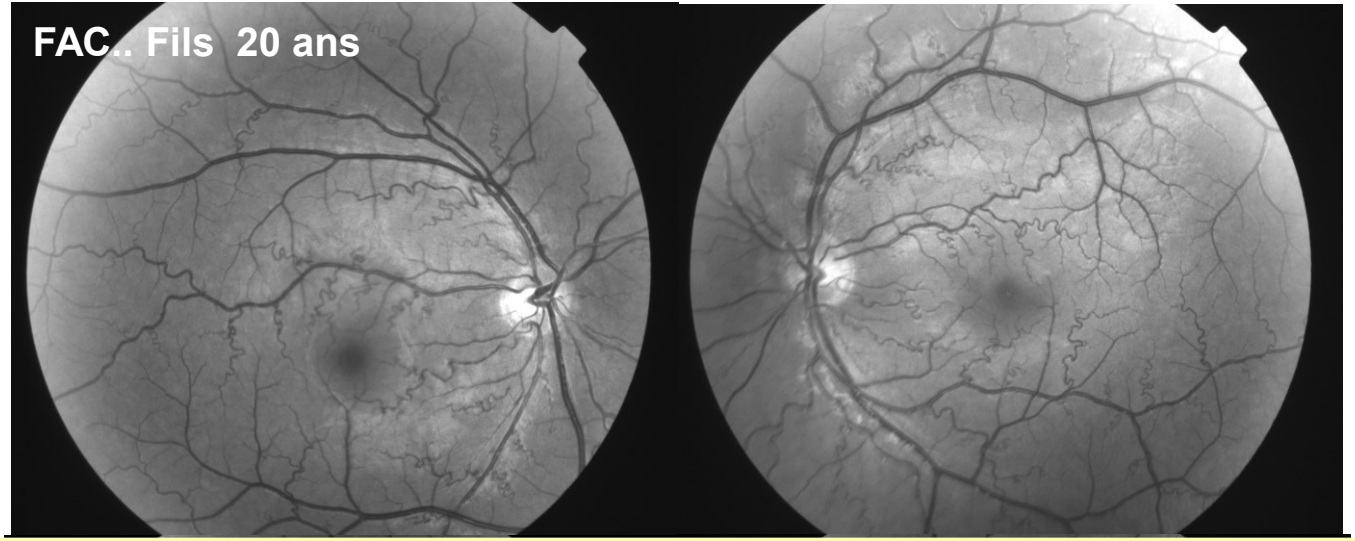


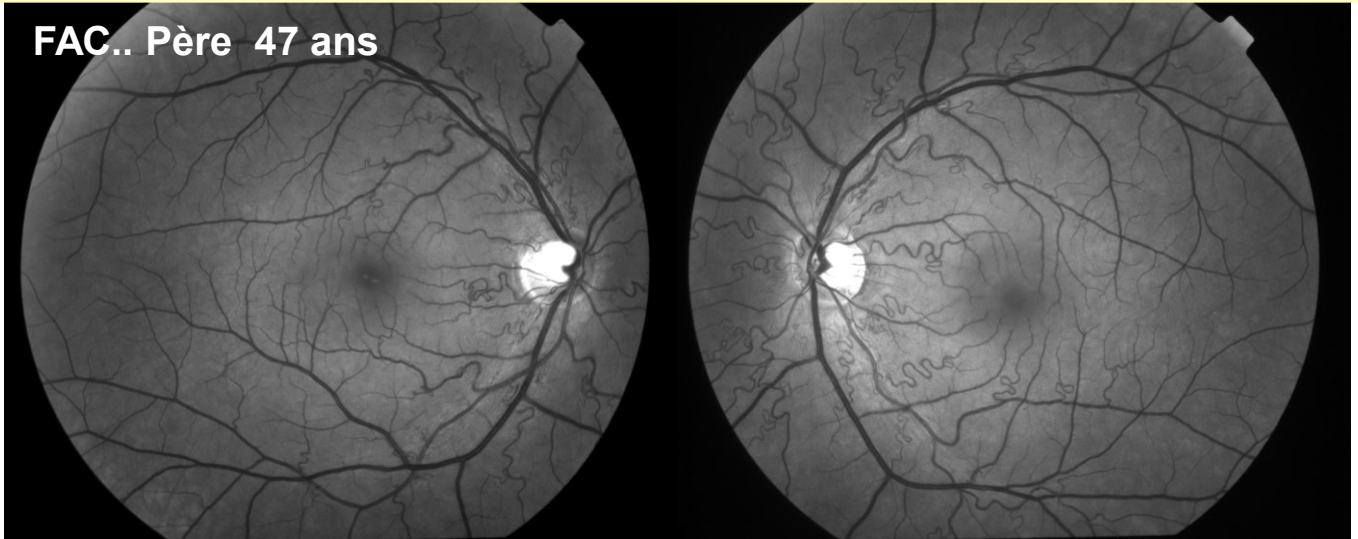
SURVEY OF OPHTHALMOLOGY VOLUME 48 • NUMBER 3 • MAY–JUNE 2003

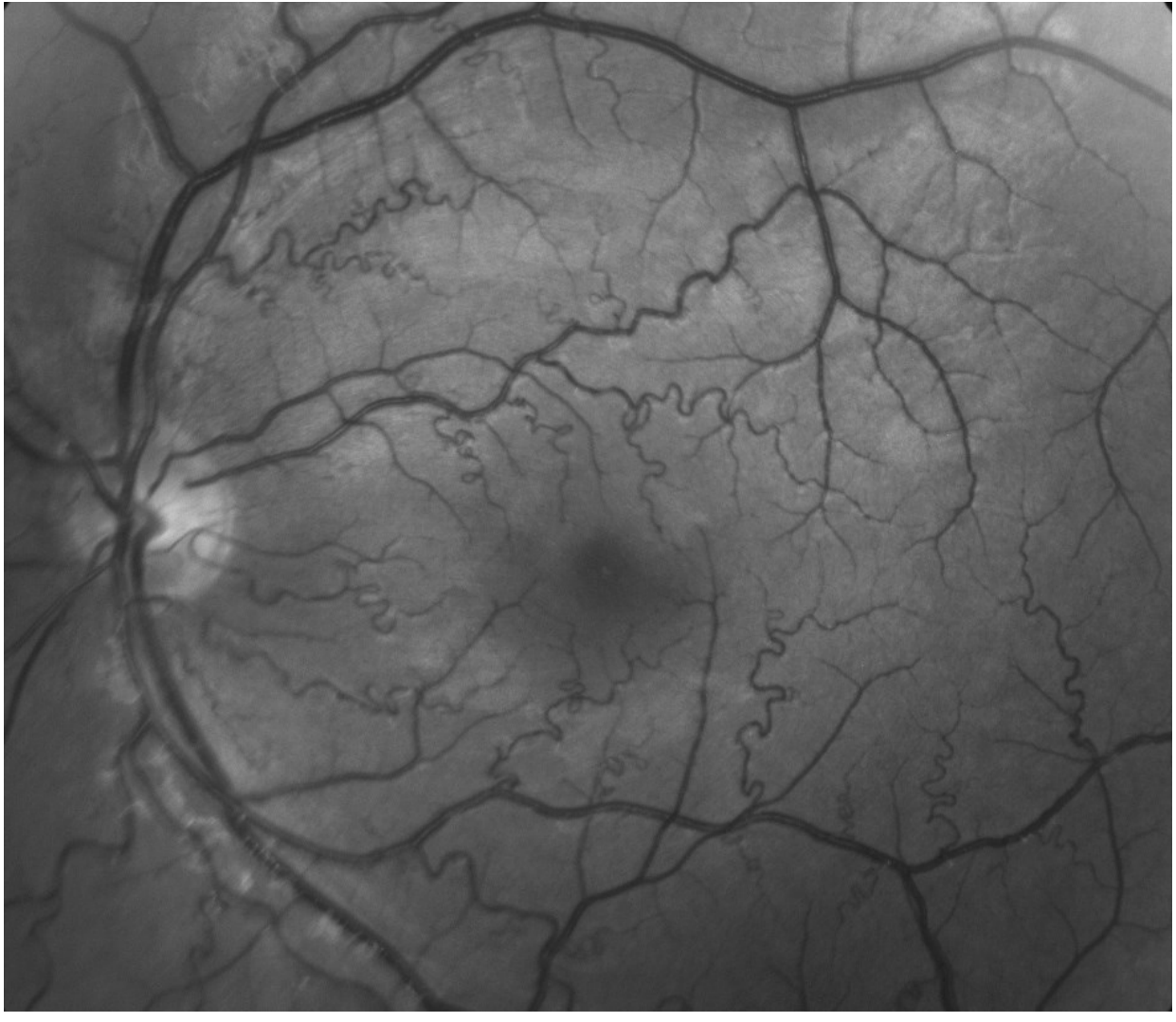
MAJOR REVIEW

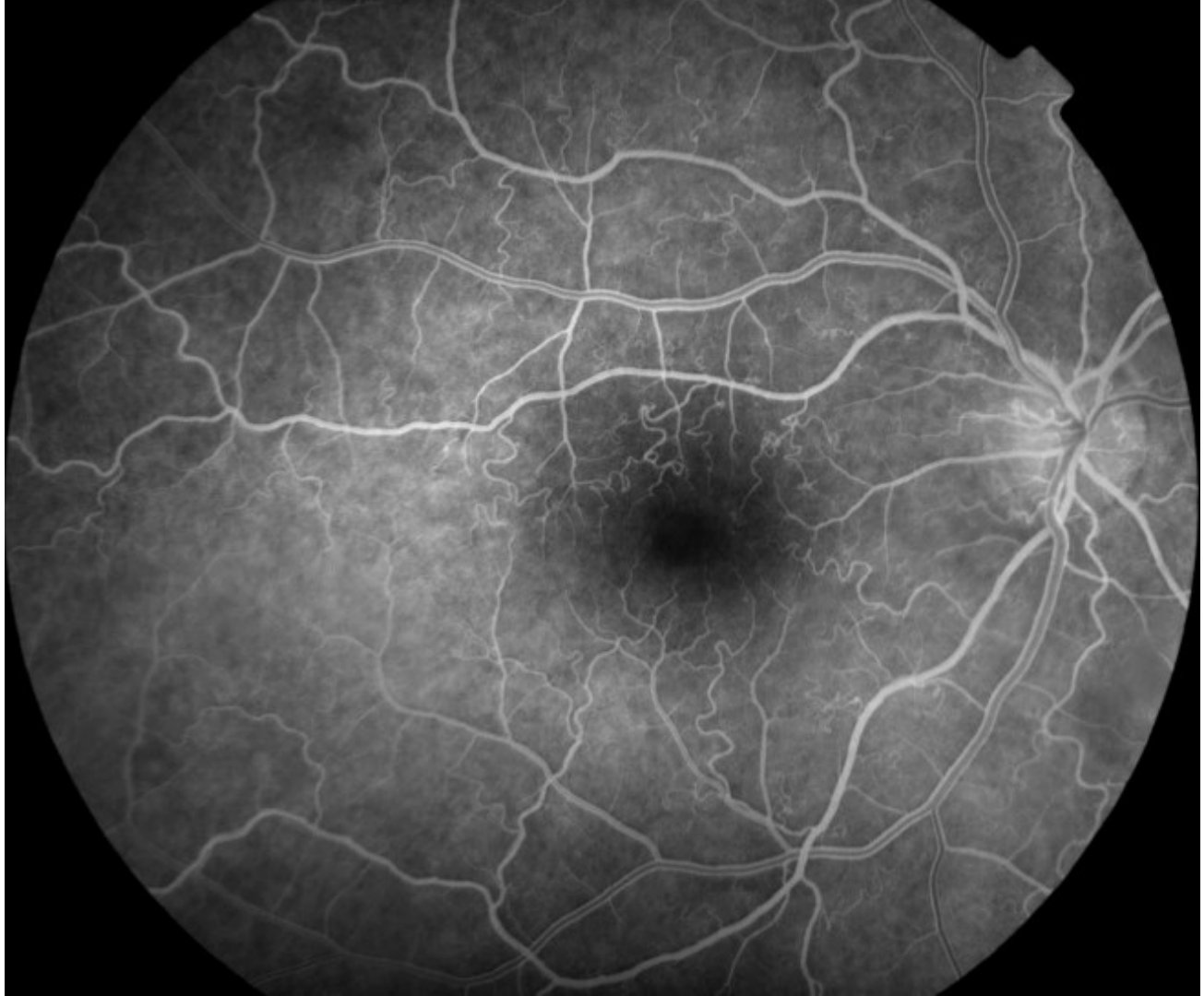
Familial Retinal Arteriolar Tortuosity: A Review

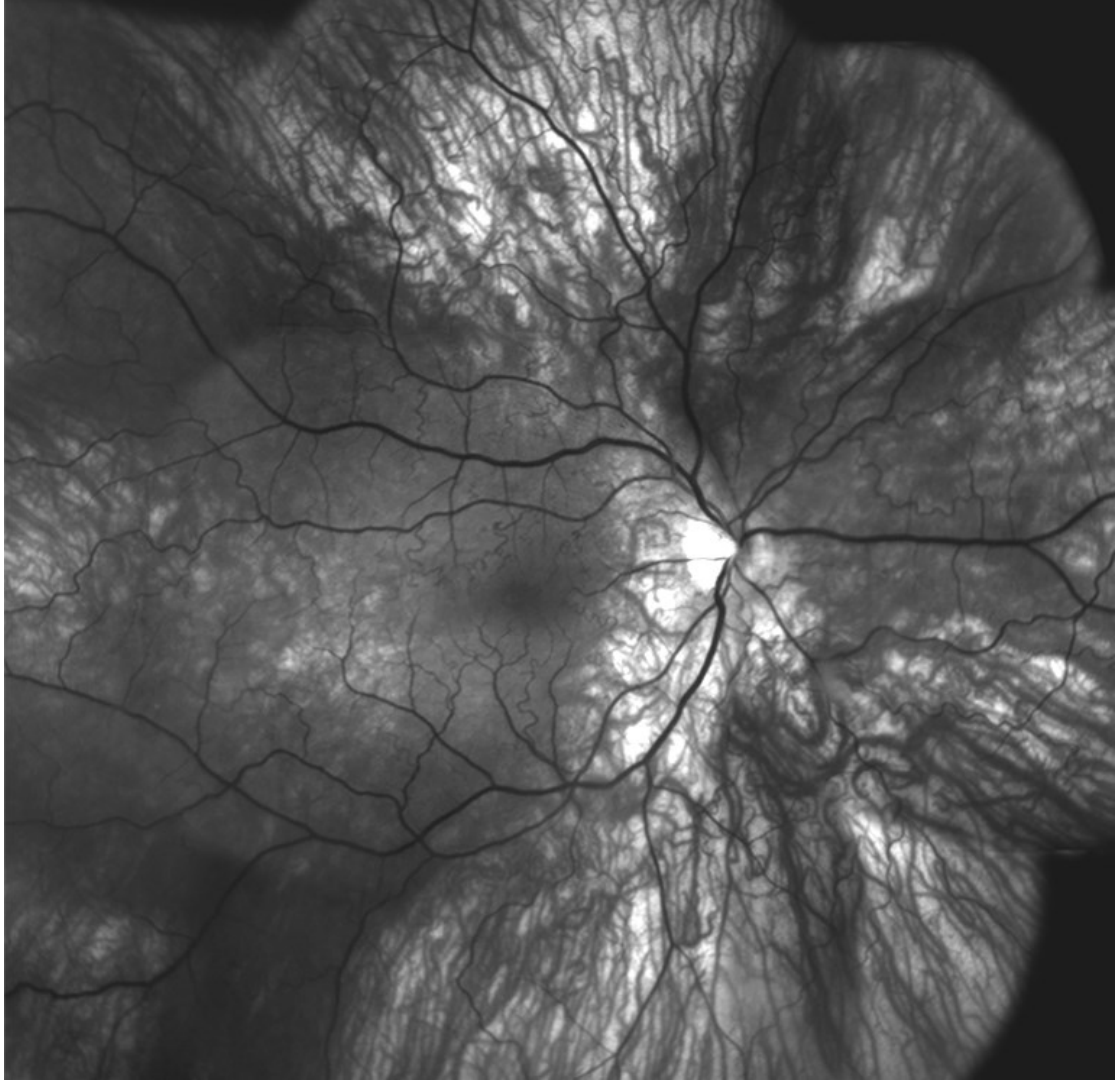
Florian K. P. Sutter, MD, and Horst Helbig, MD

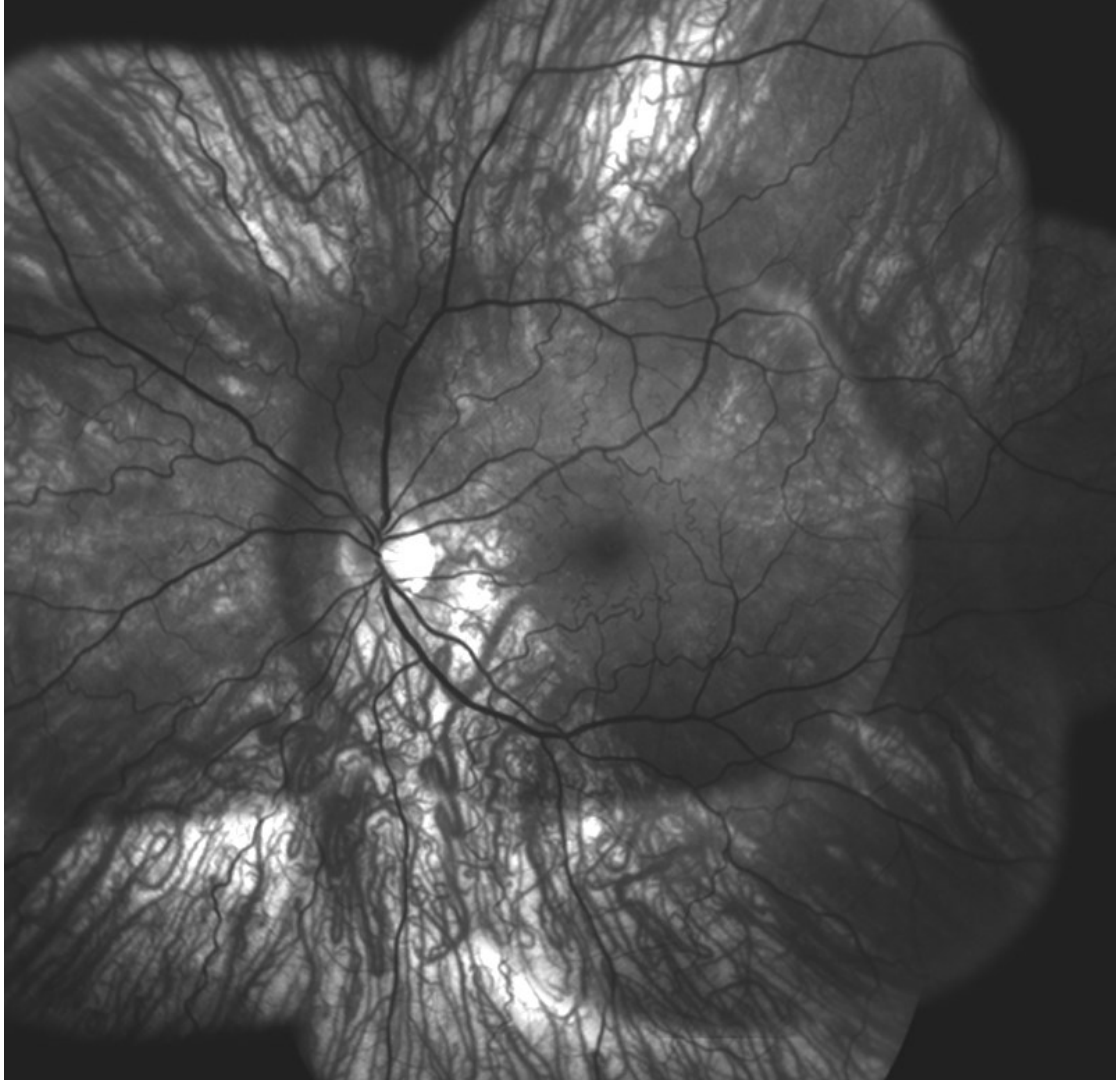

FAC.. Fils 20 ans


FAC.. Père 47 ans





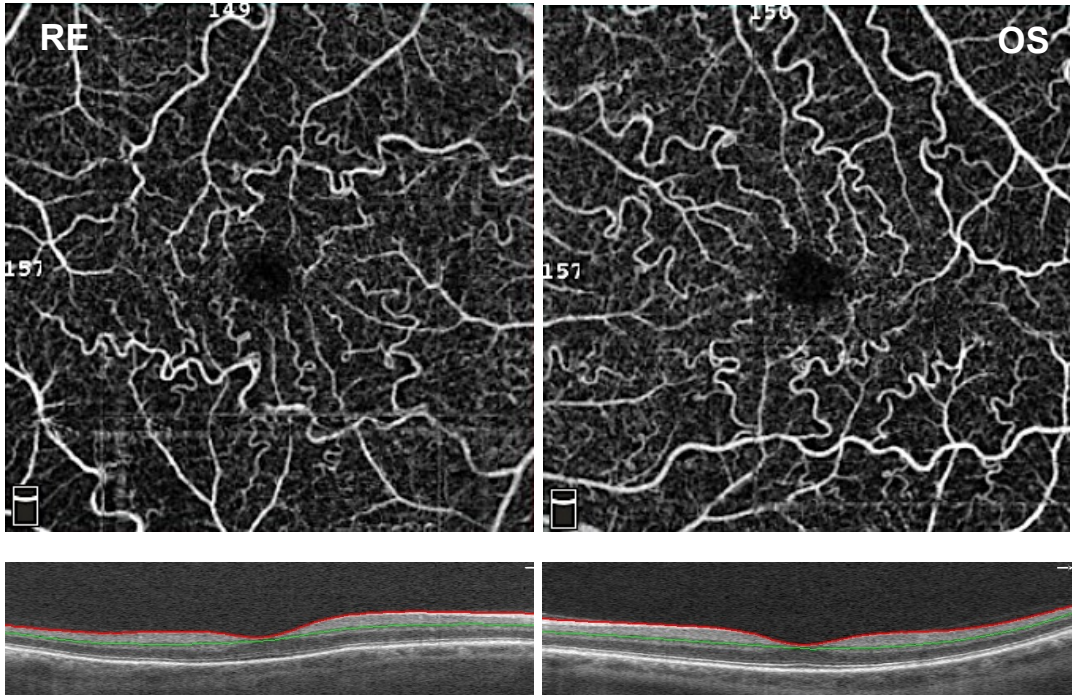




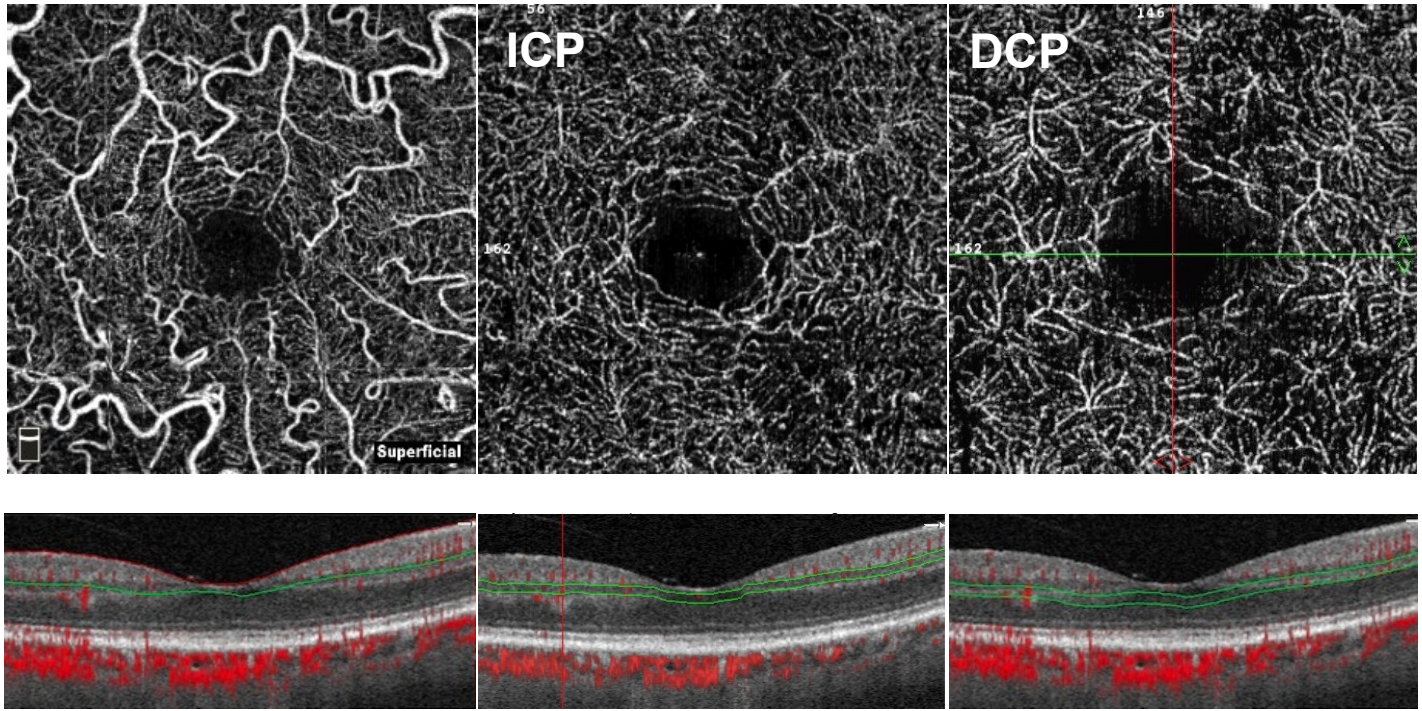
Optical Coherence Tomography Angiography of Familial Retinal Arteriolar Tortuosity

Audrey Giocanti-Auregan, MD, PhD; Alain Gaudric, MD; Frédérique Buffon, MD; Manuele Mine, MD; Corinne Delahaye-Mazza, MD; Salomon Y. Cohen, MD, PhD; Ali Erginay, MD; Hugues Chabriat, MD, PhD; Elisabeth Tournier Lasserve, MD, PhD; Valérie Krivosic, MD

- En OCTA, on retrouve l'aspect typique des TAR au niveau du SVP
- Celui-ci est bien visible jusqu'à l'extrémité des vaisseaux au niveau de la ZAC



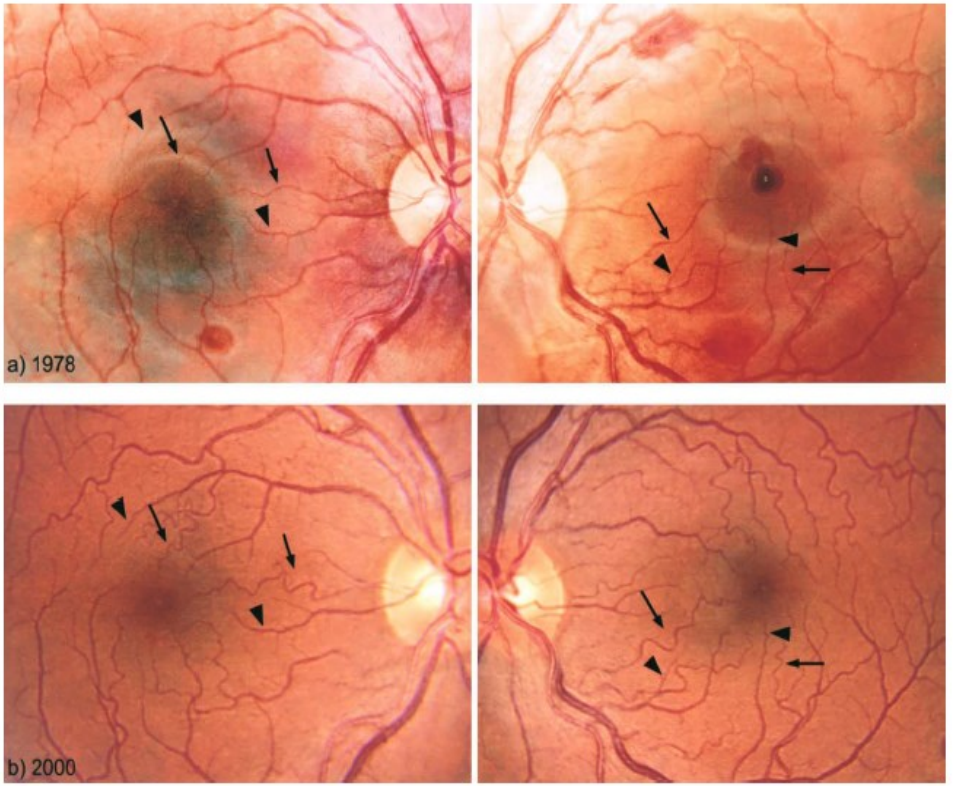
- Les plexus profonds sont épargnés

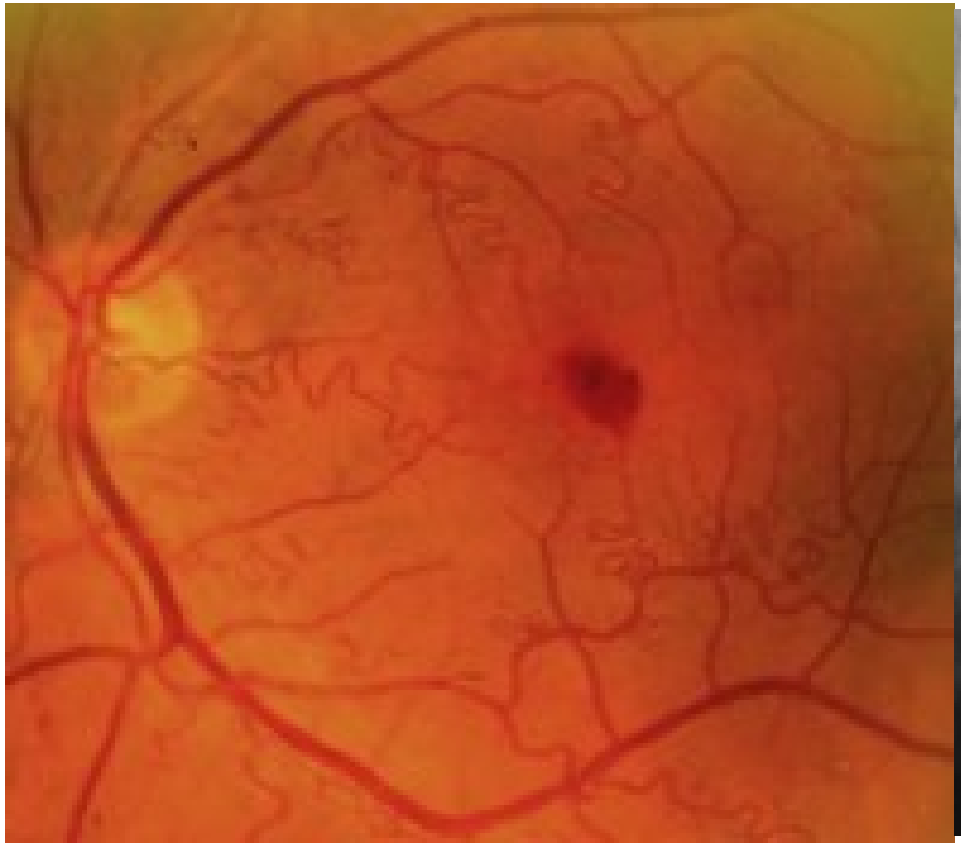


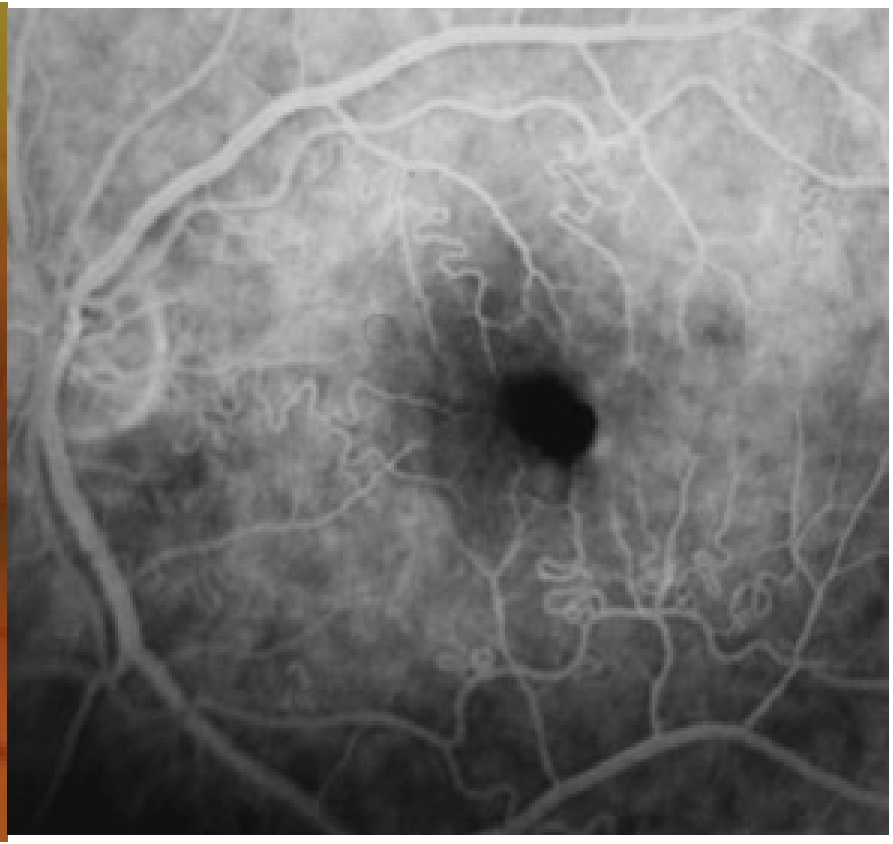
Évolution

- Hémorragies maculaires spontanées
  - régressives sans séquelles

- Majoration de l'aspect tortueux des artères avec l'âge
  - mais habituellement présentes dès l'enfance dans les examens systématiques des familles







Diagnostics différentiels

Dans les TAR, la majoration de la tortuosité ne concerne que les artérioles

TABLE 2

List of Differential Diagnoses of Increased Vascular Tortuosity of the Retina

Generalized Tortuosity (arterial and venous vasculature)	
Hyperopia, idiopathic generalized tortuosity, retinopathy of prematurity, epiretinal membranes	
Predominantly Venous Tortuosity	
Venous congestion	Cardiopulmonary disease, hyperviscosity syndromes, compressive optic neuropathy,[24] pseudotumor cerebri, central retinal vein occlusion, branch retinal vein occlusion, primary antiphospholipid syndrome[12]
Retinal ischemia	Diabetic retinopathy, high altitude retinopathy[49]
Other etiologies	Fetal alcohol syndrome[56]
Predominantly Arterial Tortuosity	
Increased blood flow	Aortal coarctation,[17,23,28] anemia,[1] sickle cell retinopathy, carotid cavernous sinus fistula,[26] localized feeder vessels (tumors, Coats disease, von Hippel-Lindau disease)
Other etiologies	Tortuosity as a sign of an arteriosclerotic disorder[36]
Rare Etiologies of Increased Retinal Tortuosity	
Renue-Osler syndrome, Aarskog syndrome,[44] Bonnet-Dechaume-Blanc syndrome[34] (syn. Wyburn-Mason syndrome[25]), neurofibromatosis type 1,[37] fascioscapulohumeral muscular dystrophy[19,39,62]	

TAR et mutation des gènes COL4A1 et A2

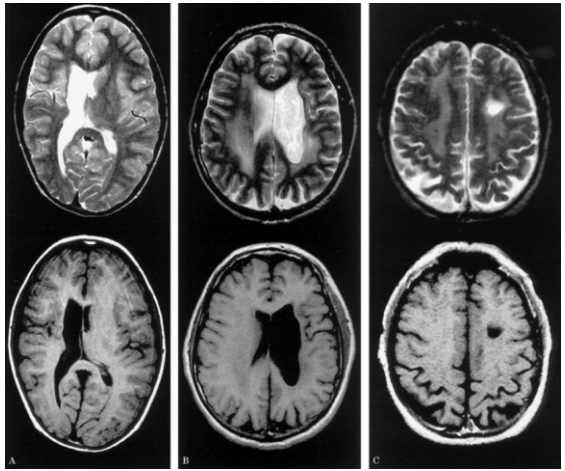
- Description récente d'association à une atteinte des petits vaisseaux cérébraux (SVD)

  Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy, Vahedi K, Neurology 2003

  Gould DB, Phalan FC, Breedveld GJ, et al. Mutations in Col4a1 cause perinatal cerebral hemorrhage and porencephaly. Science. 2005

- Et rénaux (syndrome de HANAC)

  COL4A1 Mutations and Hereditary Angiopathy, Nephropathy, Aneurysms, and Muscle Cramps, E.Plaiser and col, NEJM 2007



- COL4A2

  COL4A2 mutation causing adult onset recurrent intracerebral hemorrhage and leukoencephalopathy. Gunda B, Mine M, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Audrezet MP, Tournier-Lasserve E. J Neurol. 2014

EAN GUIDELINE

Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology

M. Mancuso[a], M. Arnold[b], A. Bersano[c], A. Burlina[d], H. Chabriat[e], S. Debette[f], C. Enzinger[g], A. Federico[h], A. Filla[i], J. Finsterer[j], D. Hunt[k], S. Lesnik Oberstein[l], E. Tournier-Lasserve[m] and H. S. Markus[n]

Genetic testing

- Missense variants of *COL4A1* or *COL4A2* leading to replacement of a glycine of a gly-x-y motif in the triple helix and variant leading to premature stop codon are pathogenic.
- Variants of *COL4A1* at the binding site of mir-29 microRNA within COL4A1 3'UTR can cause a distinct ischaemic cSVD with early onset in adults called PADMAL.

Management

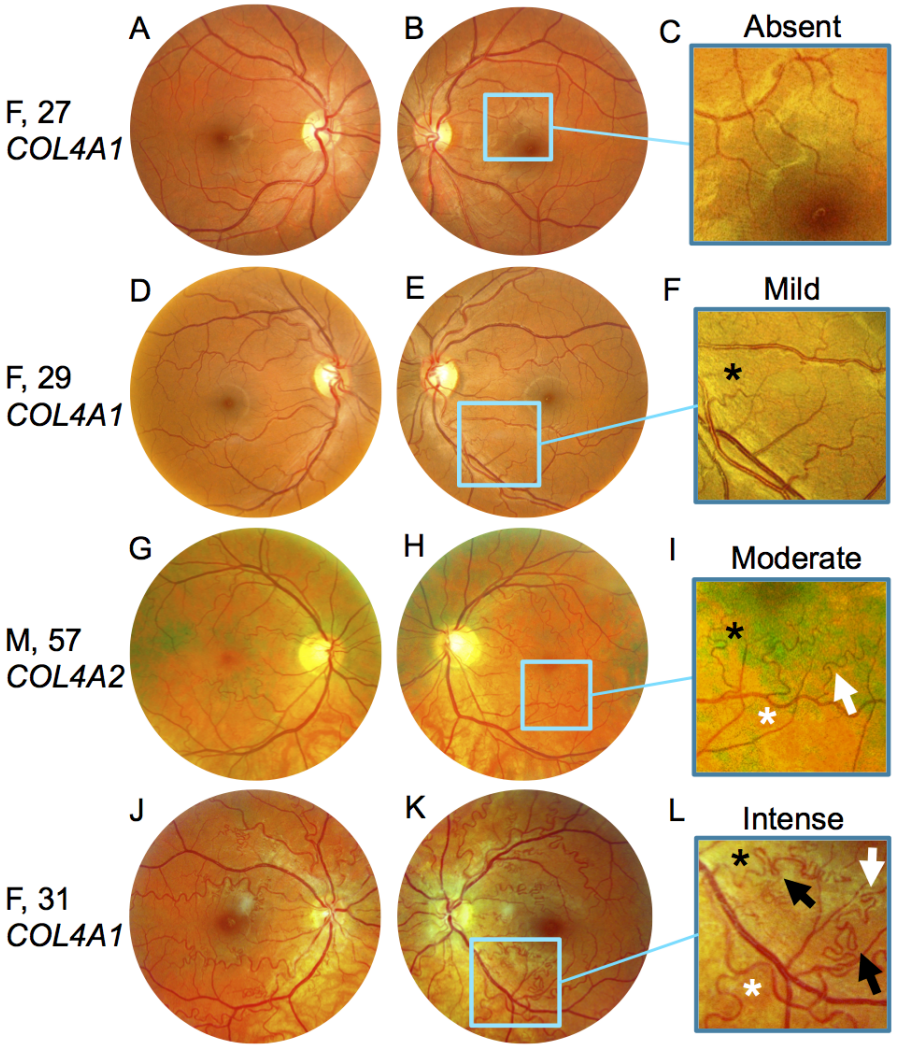
- Antiplatelet and anticoagulant treatments are not recommended in *COL4A1*/2 cSVD.
- Intravenous thrombolysis is not recommended in *COL4A1*/2 cSVD.
- Sporting activities with a high risk of head trauma or excessive or prolonged exercise should be avoided.
- A Caesarean section should be considered in women giving birth where the foetus harbours a *COL4A1*/2 mutation.

Monogenic cerebral SVD

- cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)
- Autosomal dominant High Temperature Requirement A Serine Peptidase 1 (HTRA1)
- cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL)
- pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL)
- Fabry disease, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
- type IV collagen (COL4)A1/2

TAR et mutation des gènes COL4A1 et A2

- Dans une cohorte de patients (indexes et apparentés) présentants une leucoencéphalopathie et une mutation COL4A1 ou A2
- 50% présentaient le phénotype TAR



Que sait on des gènes COL4A1 et A2

- Codent pour le collagène de type IV qui est un élément de soutient de la membrane basale des artérioles
- Les mutations de ces gènes vont donc fragiliser la paroi vasculaire…. Et rendre possible la survenue de petits saignements dans la rétine, le cerveau, les reins…..

Phenotype related to COL4A1 and A2 mutation

- Familial retinal arteriolar tortuosity
- Axenfeld-Rieger syndrome
- Porencephaly
- Cerebral small vessel disease with or without ocular abnormalities
- Susceptibility to intracerebral hemorrhage
- Nephropathy, muscle cramps

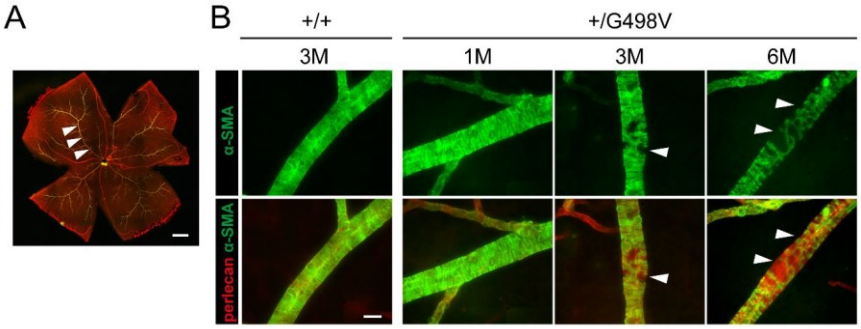
Que sait on des gènes COL4A1 et A2

- COL4A 1/2 encodes type IV collagen which is a supporting element of the basement membrane of arterioles
- The mutations of these genes will therefore weaken the vascular wall

Severity of arterial defects in the retina correlates with the burden of intracerebral haemorrhage in COL4A1-related stroke

Julien Ratelade[1], Nicolas Mezouar[1], Valérie Domenga-Denier[1], Ambre Rochey[1], Emmanuelle Plaisier[2,3] and Anne Joutel[1,4*] J Pathol . 2018

- Loss of smooth muscle cells in arteries in mutant mice could explain :
  - the increased tortuosity
  - the occurrence of hemorrhage after minor trauma



Conclusion

- Du fait du risque d'hémorragie cérébrale, la découverte de tortuosités artérielles rétiniennes
  - Examiner les membres de la famille
  - Rechercher une hématurie
  - Imagerie cérébrale
  - Recherche de mutation COL4A1 ou A2

- *Par ailleurs la présence de mutation COL4A1 ou A2 exposerait au risque d'hémorragie cérébrale de l'enfant en cas d'accouchement par voie basse*

Université de Paris

Centre Ophtalmologique de l'Odéon, Paris

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

vkrivosic@gmail.com

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

cervco
CENTRE DE RÉFÉRENCE DES MALADIES VASCULAIRES RARES DU CERVEAU ET DE L'ŒIL