The background image shows a large, open courtyard in front of a grand, multi-story classical building with many arched windows. In the center of the courtyard is a green lawn with a small, red metal gazebo. To the right, there is a long, low wall with several large, ornate planters containing flowers. The sky is clear and blue.

# **Hereditary non amyloid small vessel diseases of the brain: Pathological data**

**F. GRAY**

Université Paris VII

# Hereditary Diseases of Cerebral Small Vessels

## Autosomal Dominant

- CADASIL, (NOTCH3)
- Retinal vasculopathy with cerebral leukodystrophy
- COL4A1 et COL4A2 mutations
- SVD mapping to chromosome 20q13
- Swedish hMID & PADMAL

} gene +  
gene (-)

## Autosomal Recessive

- CARASIL,
- Leukoencephalopathy Calcifications and Cysts

gene +  
gene (-)

X-linked recessive : Fabry disease

gene +

Mitochondrial : MELAS

# CADASIL

## Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts & Leukoencephalopathy

- **Tournier-Lasserre E et al.** Autosomal dominant syndrome with stroke like episodes and leukoencephalopathy. *Stroke* 1991;22:1297-1302
- **Tournier-Lasserre E, Joutel A, et al.** CADASIL maps to chromosome 19q12. *Nat Genet* 1993;3:256-259
- **Joutel A et al.** Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383:707-710
- **Baudrimont M, et al.** Autosomal dominant leukoencephalopathy and subcortical ischemic stroke. A clinicopathological study. *Stroke* 1993;24:122-125

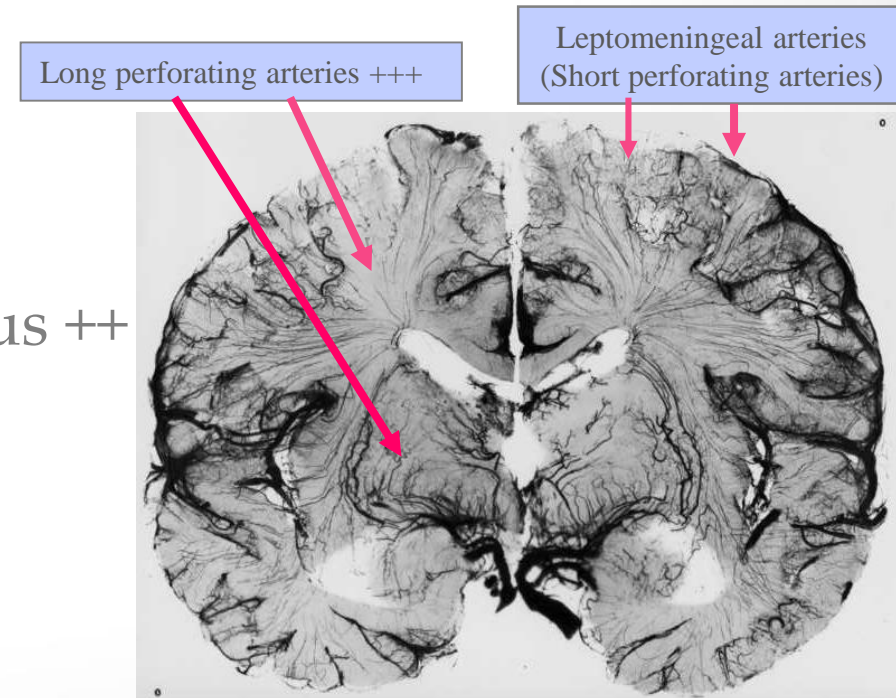
# Specific Vascular Changes

- Topography

- Diffuse but involving predominantly the CNS

- Arterioles +++

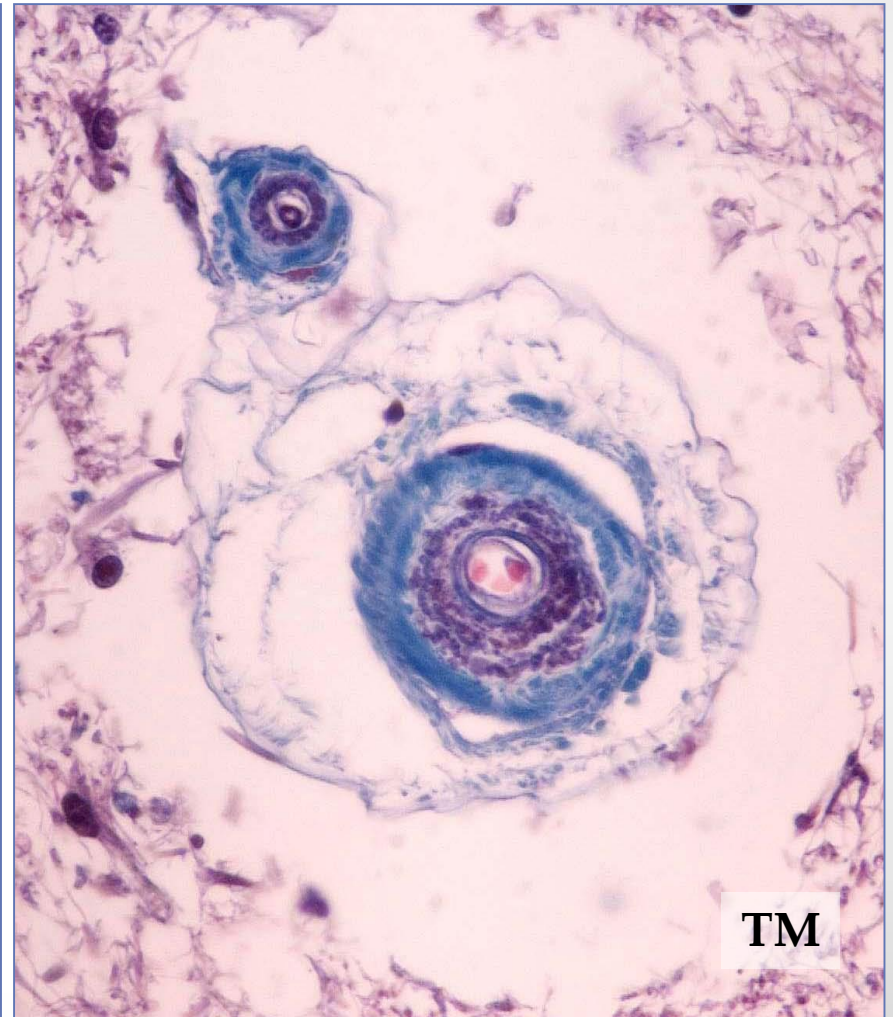
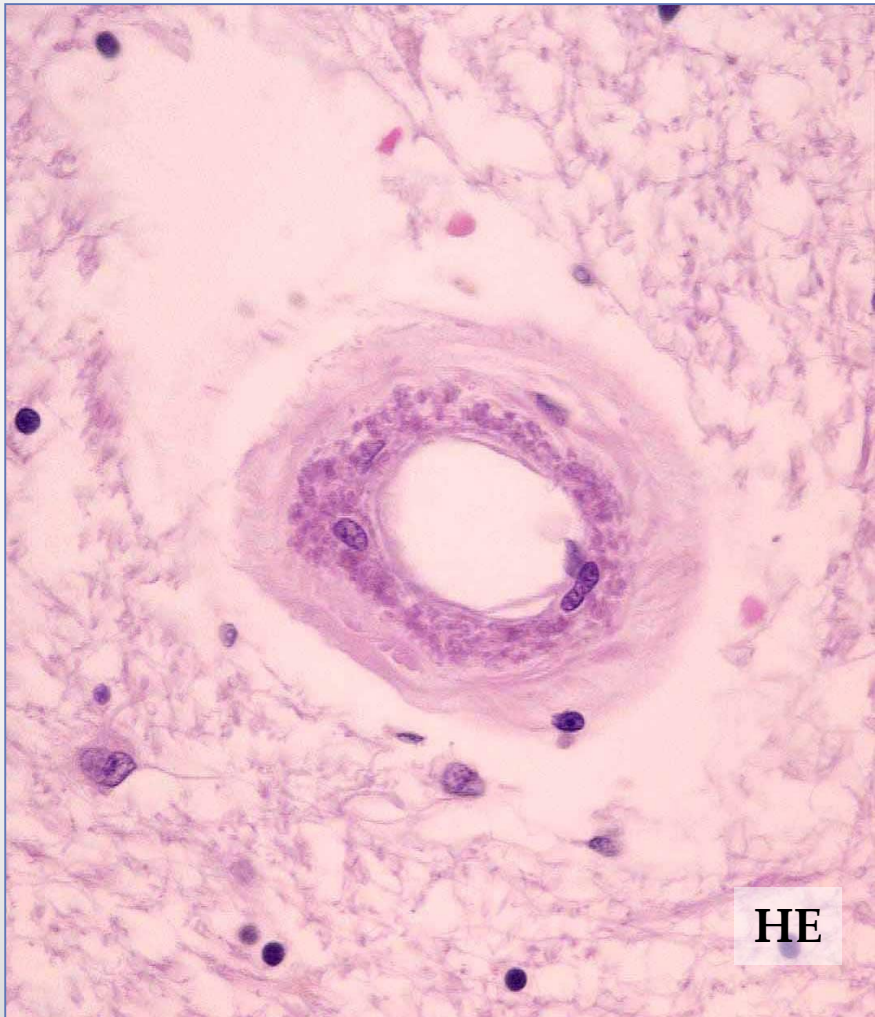
- Leptomeninges +++
    - Deep White Matter+++
    - Basal Ganglia, Thalamus ++
    - Pons ++
    - Spinal Cord +



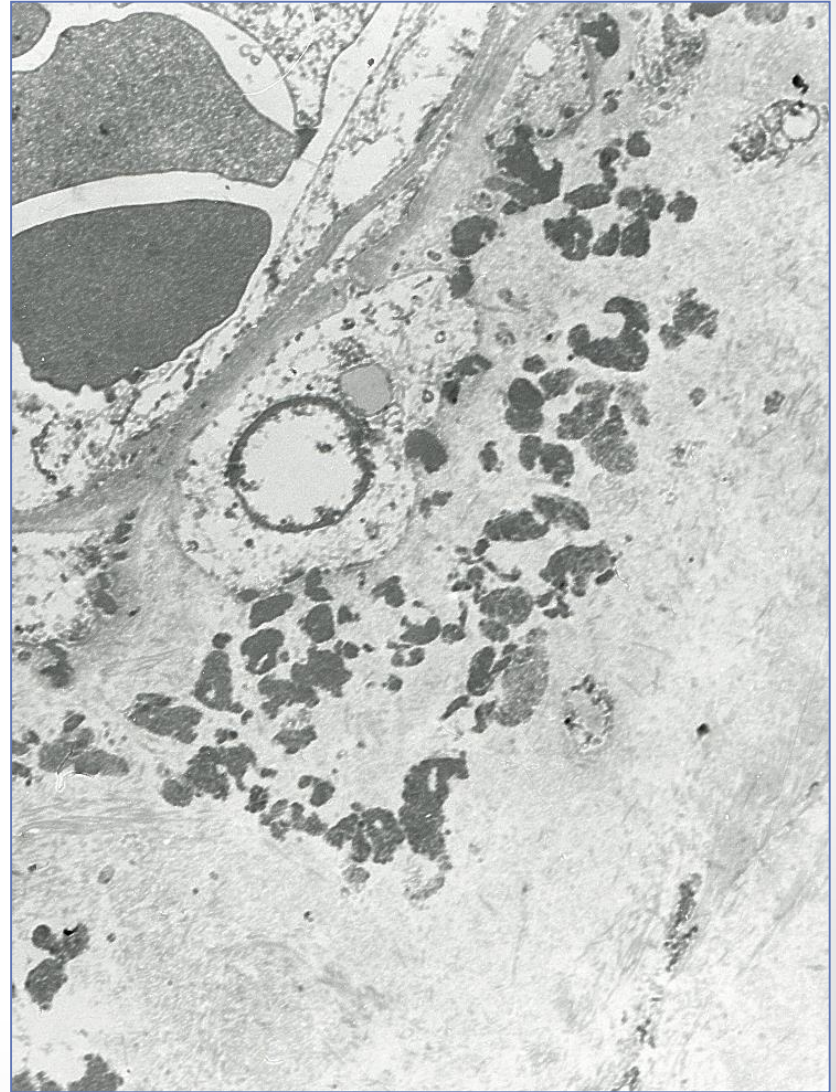
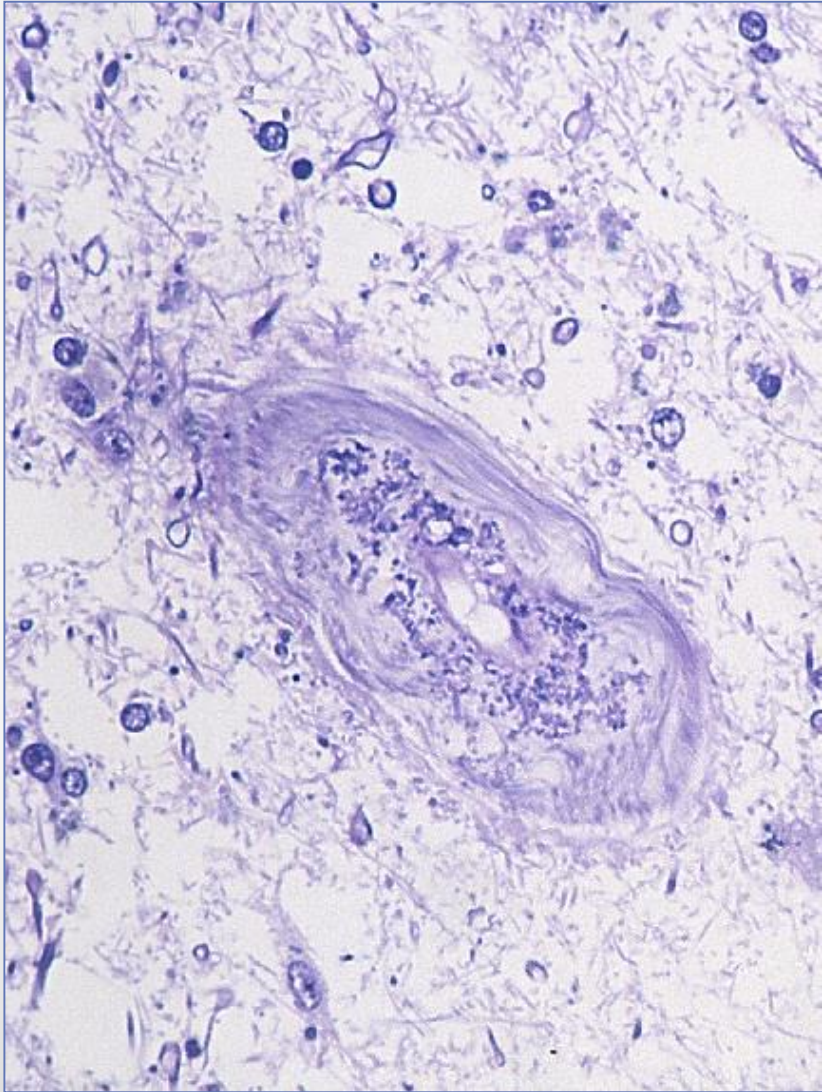
# Specific Vascular Changes

- Morphology
  - Granular basophilic deposits in the media of arterioles
  - « Granular Osmiophilic Material, GOM » by E.M.
  - Accumulation of the extracellular domain of Notch3 (ECDN3) at IHC (distinct of GOM)
  - Degeneration of smooth muscle cells in the media
  - Fibrous thickening of the arteriolar wall with stenosis of the lumen

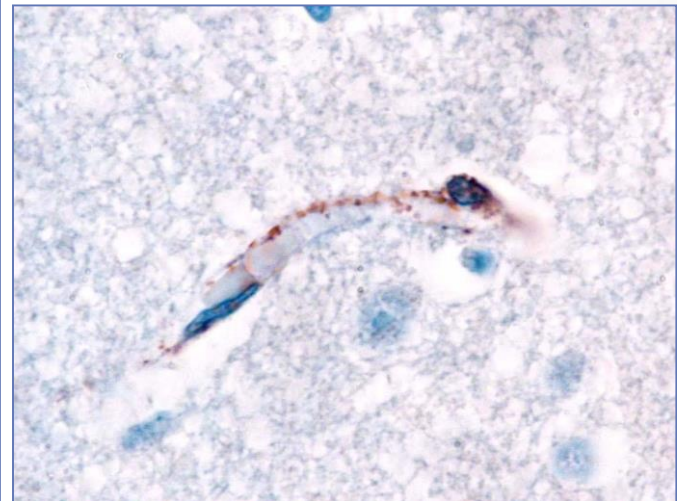
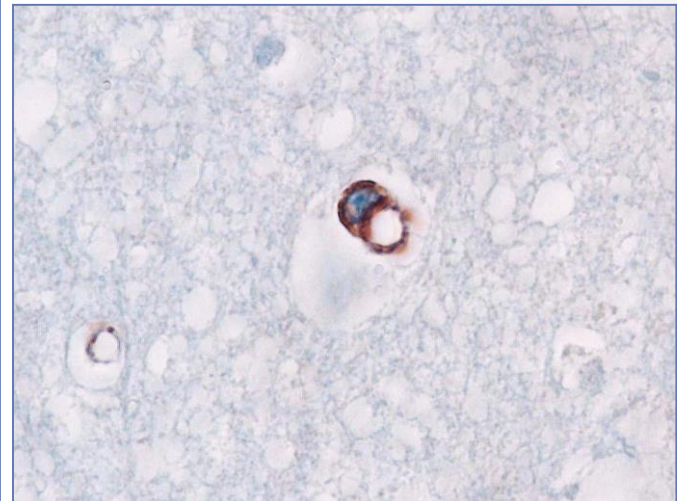
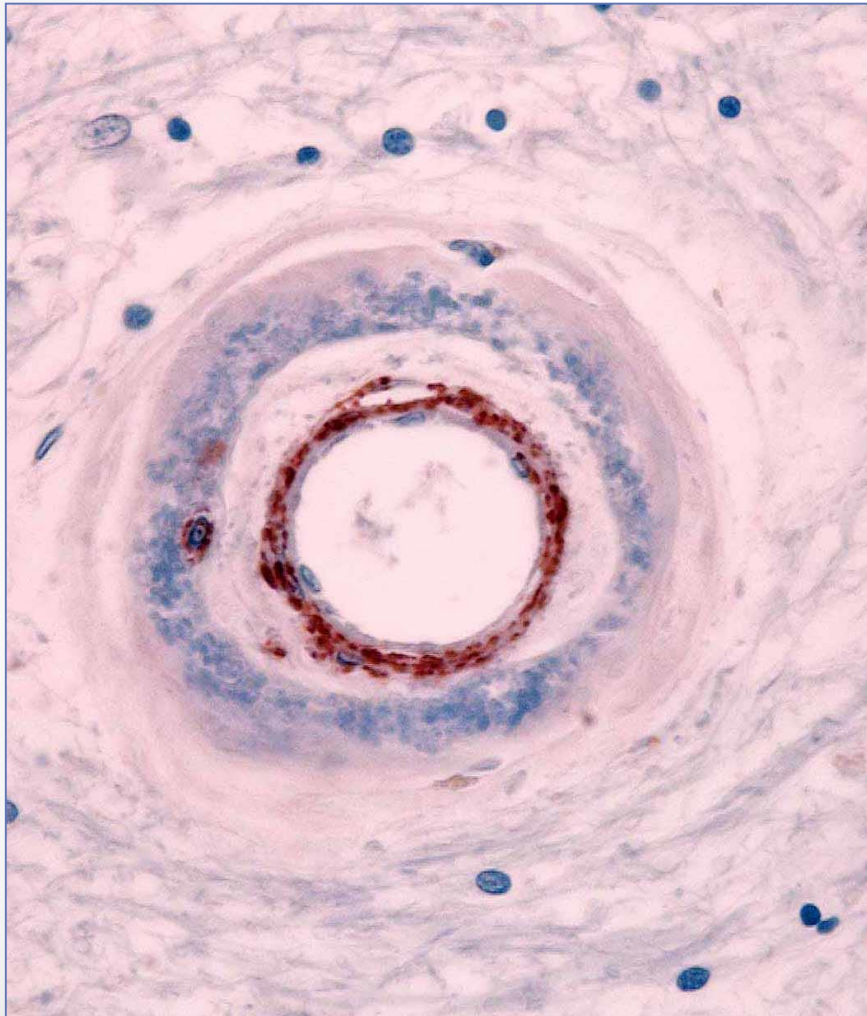
# Granular Basophilic Deposits

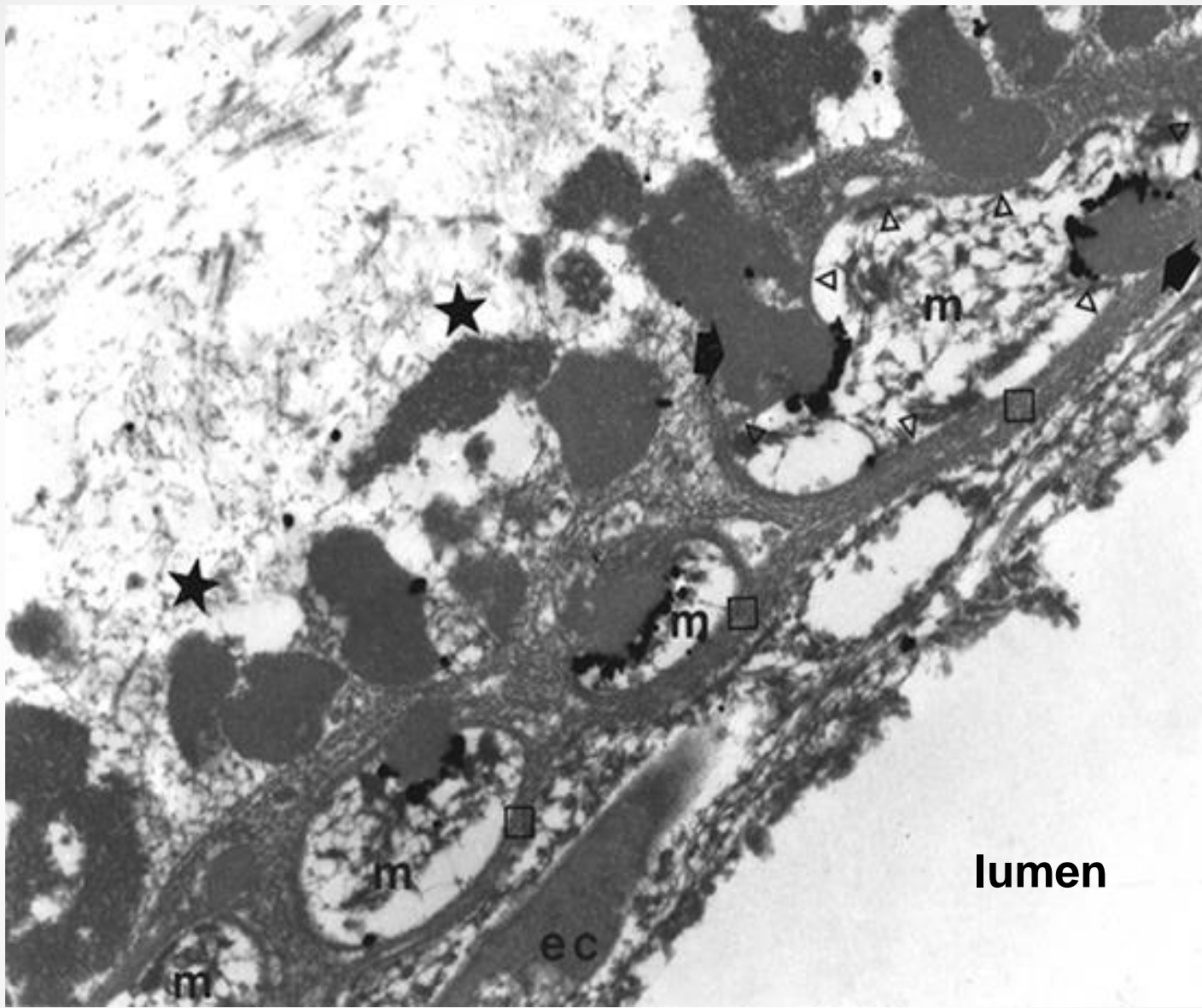


# Granular Osmiophilic Material

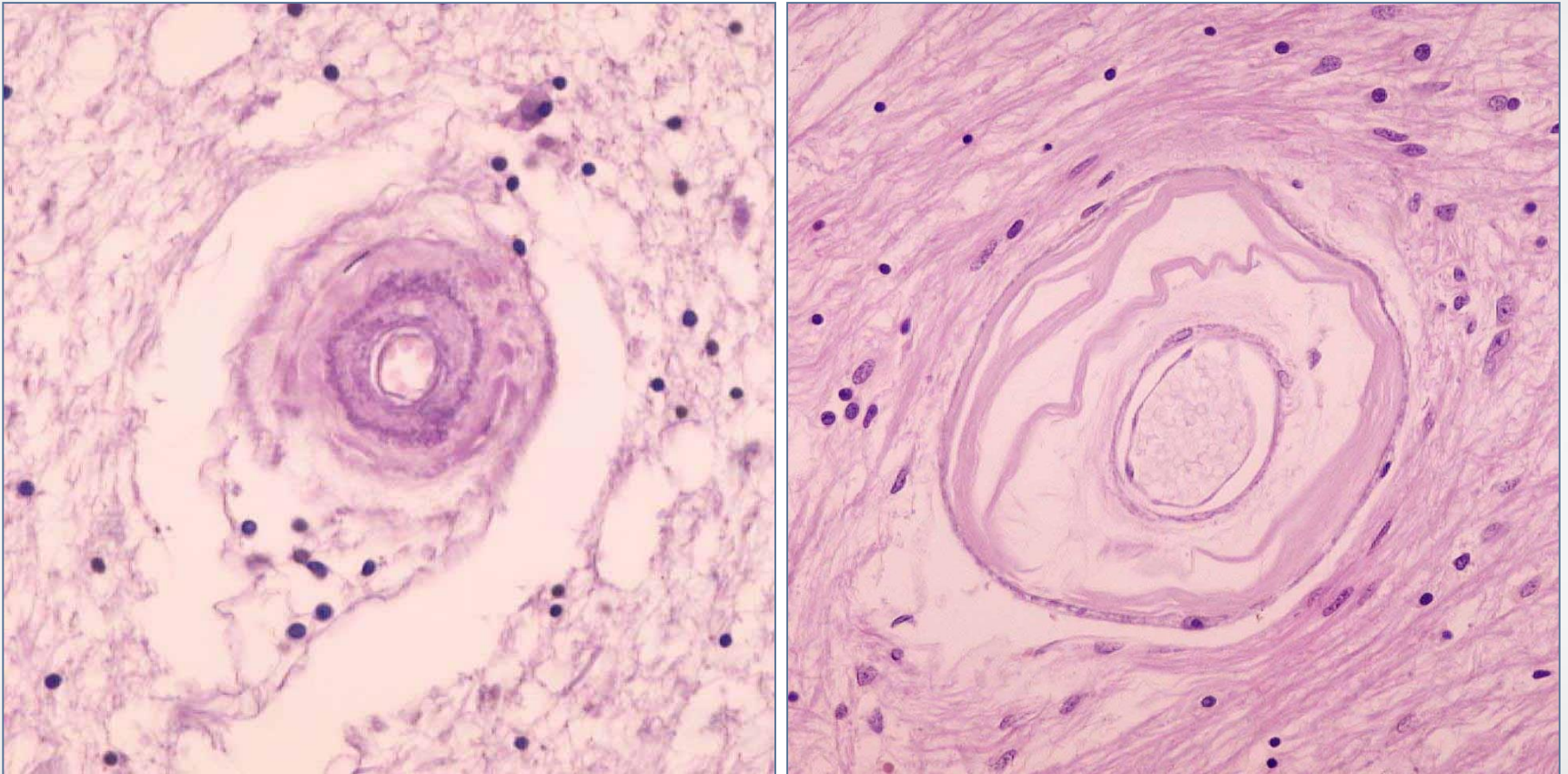


# Notch 3 ECD IHC





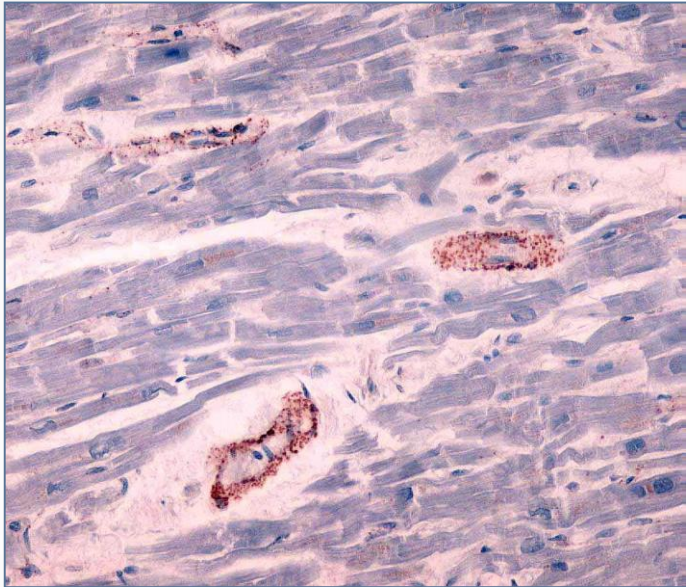
# Secondary Vascular Changes



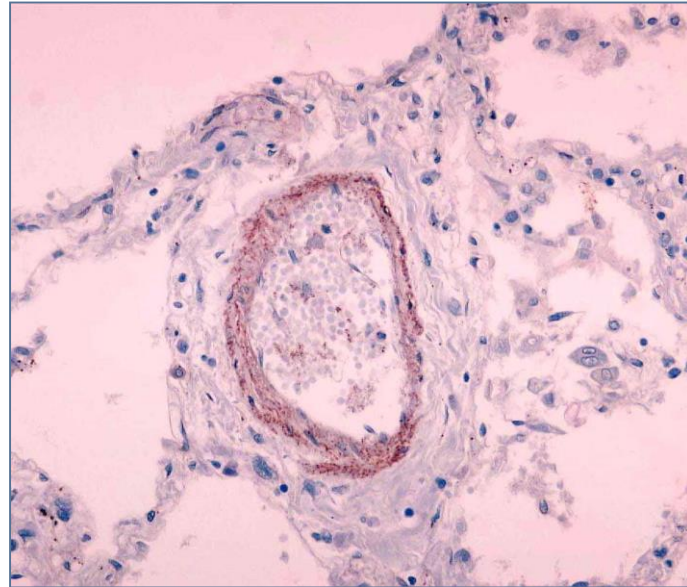
Craggs LJJ, et al. Quantitative Vascular Pathology and Phenotyping Familial and Sporadic Cerebral Small Vessel Diseases. *Brain Pathology* 2013, **23**:547-557

# Extracerebral Vascular Changes

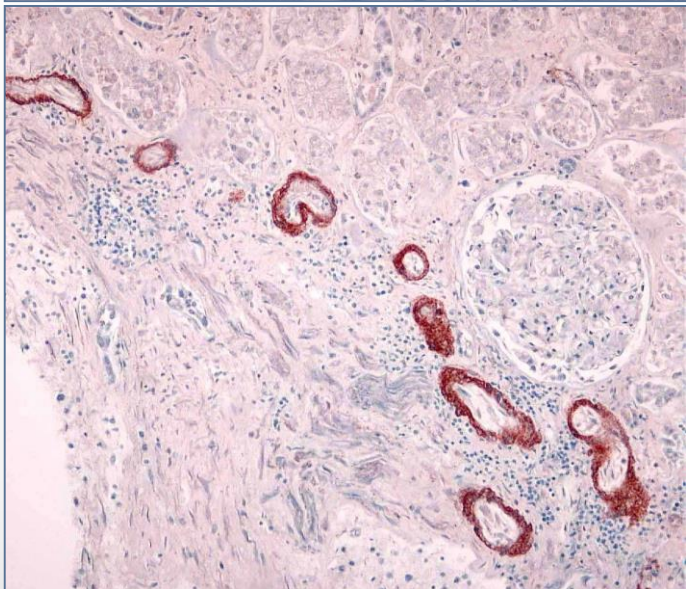
Heart



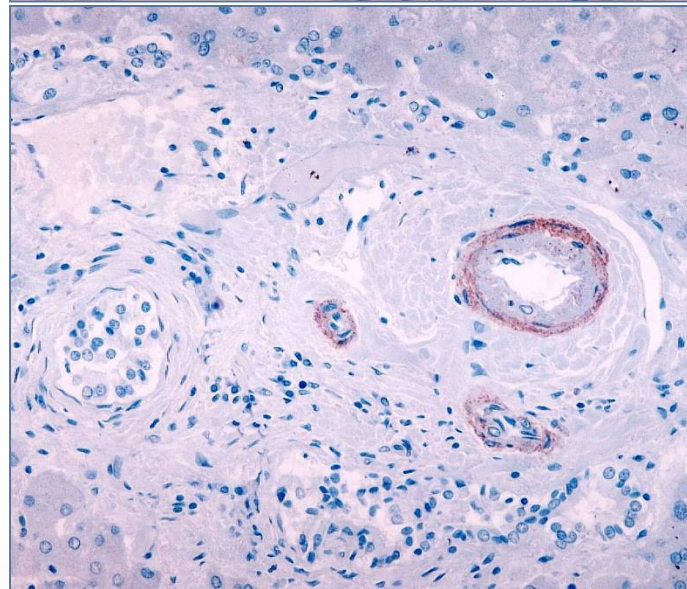
Lung



Kidney

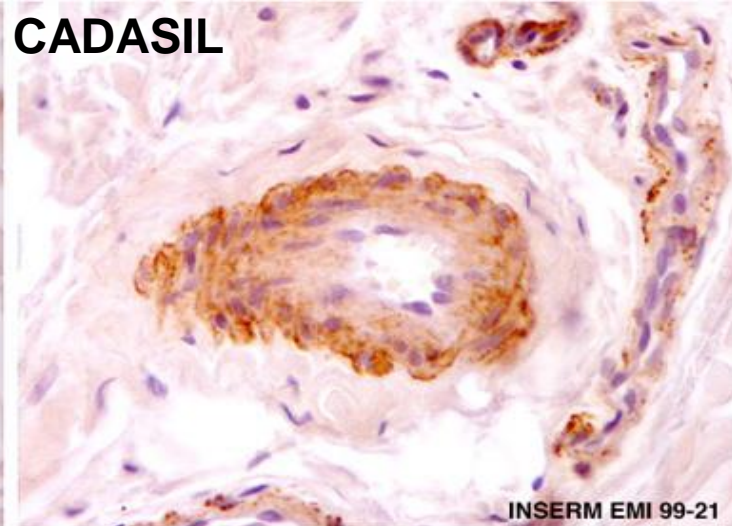
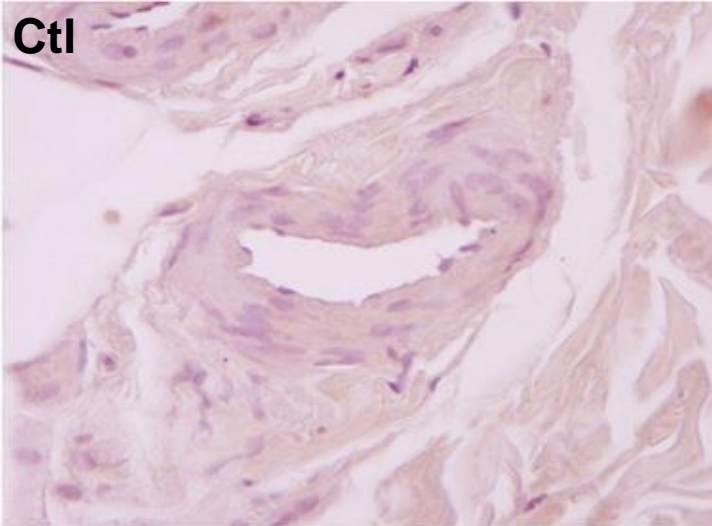
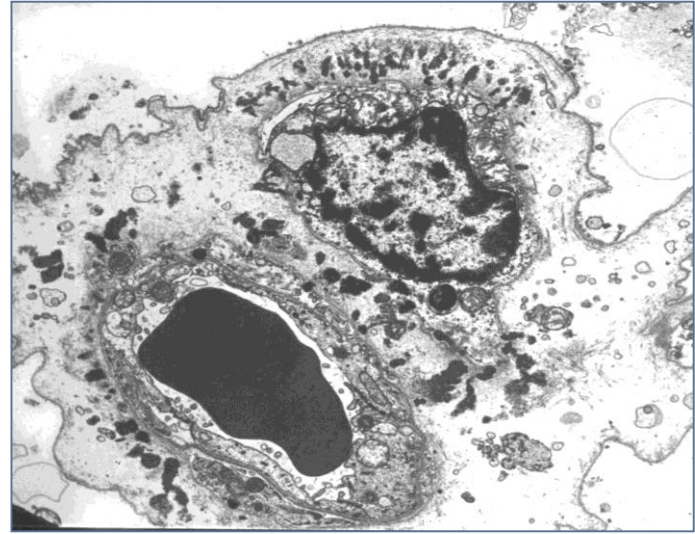
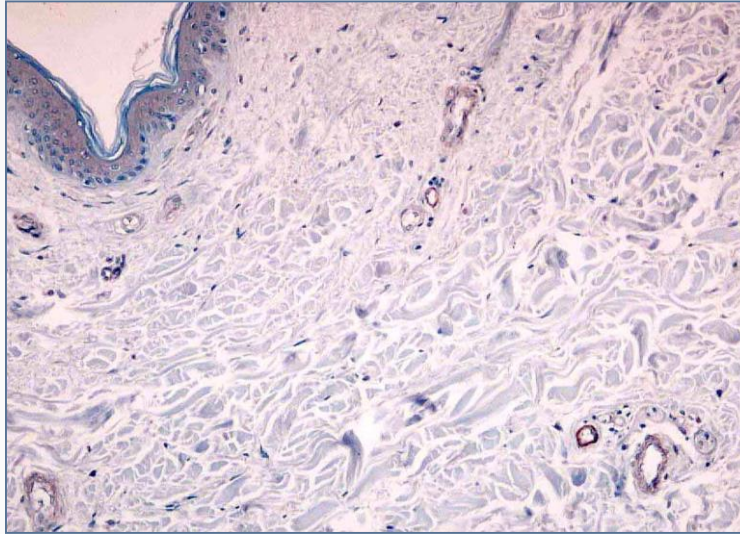


Liver



# Extracerebral Vascular Changes

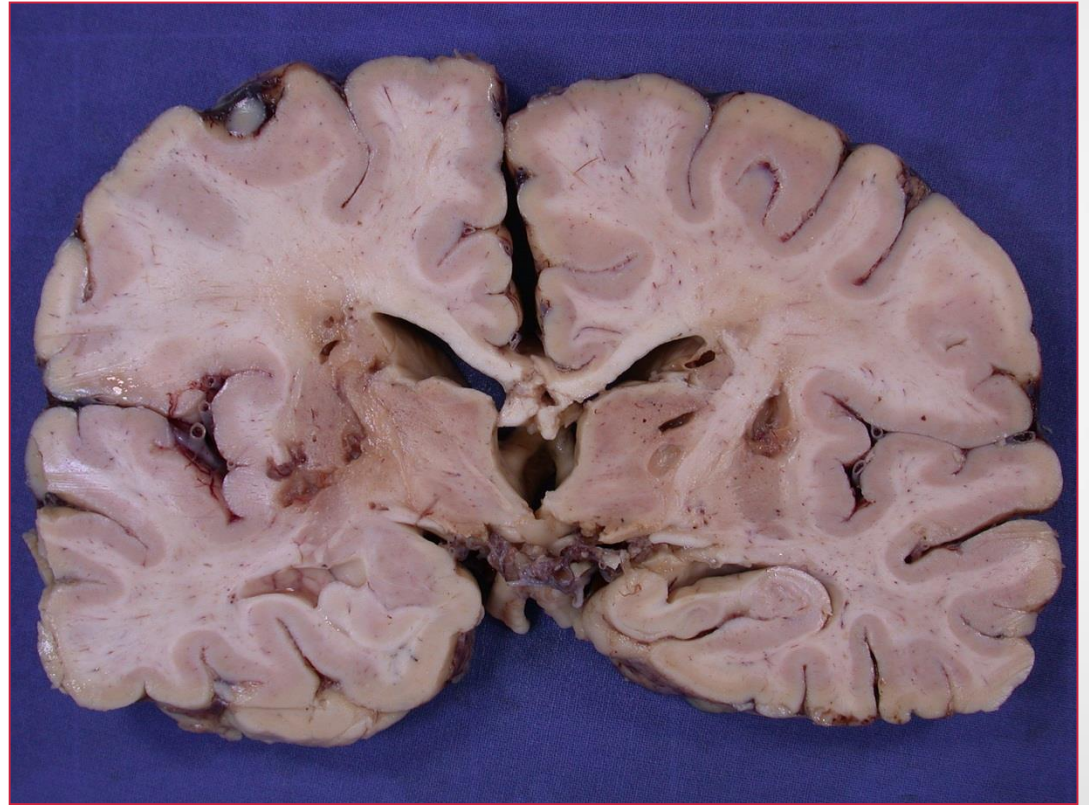
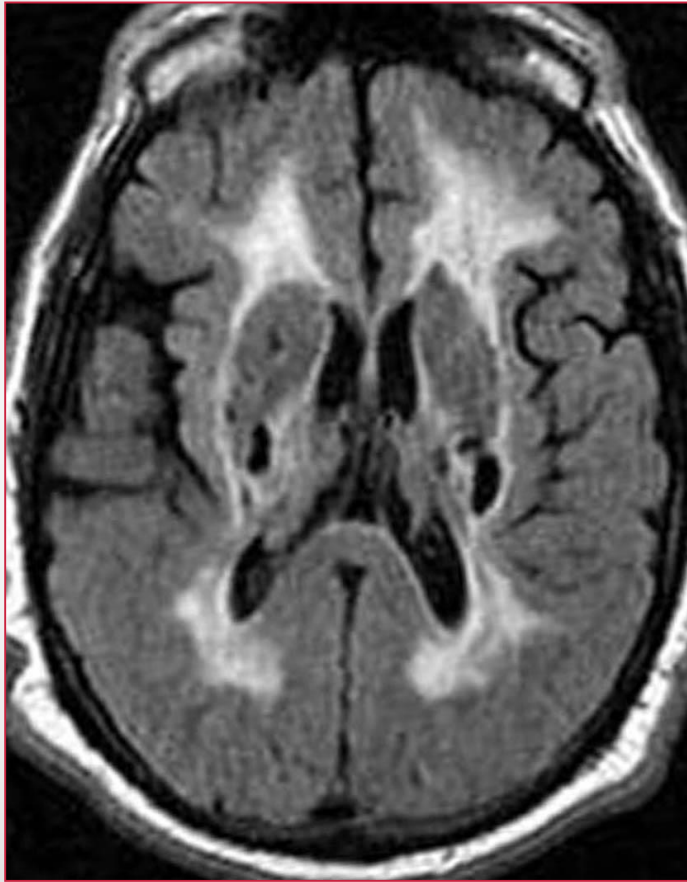
Skin



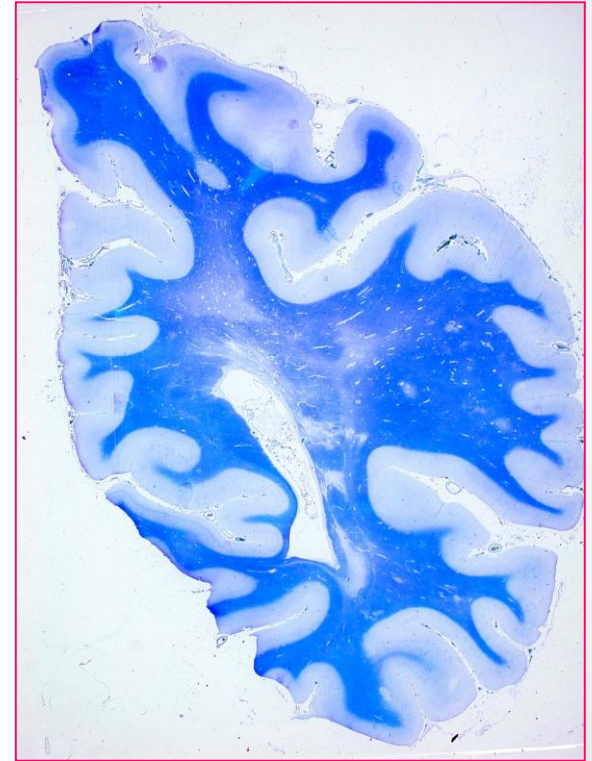
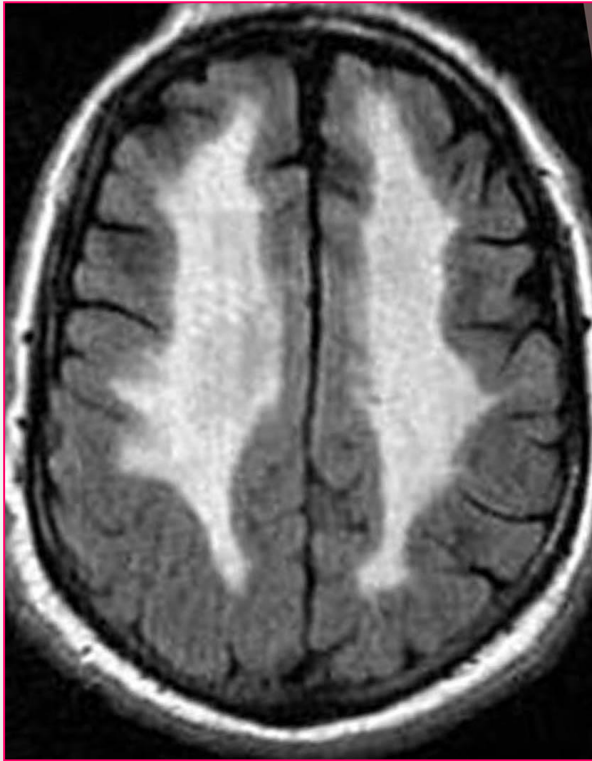
# Secondary Brain Changes

- **Lacunar Infarcts** (WM +++, BG +++, Brainstem ++, Thalamus +, Cerebellum +)
- **Leukoencephalopathy**
- **Haemorrhages** (uncommon)
- **Status cribrosus**  
(BG, Thalamus, subcortical U fibres)
- **Involvement of the cerebral cortex**  
(considered uncommon)

# Lacunar Infarcts

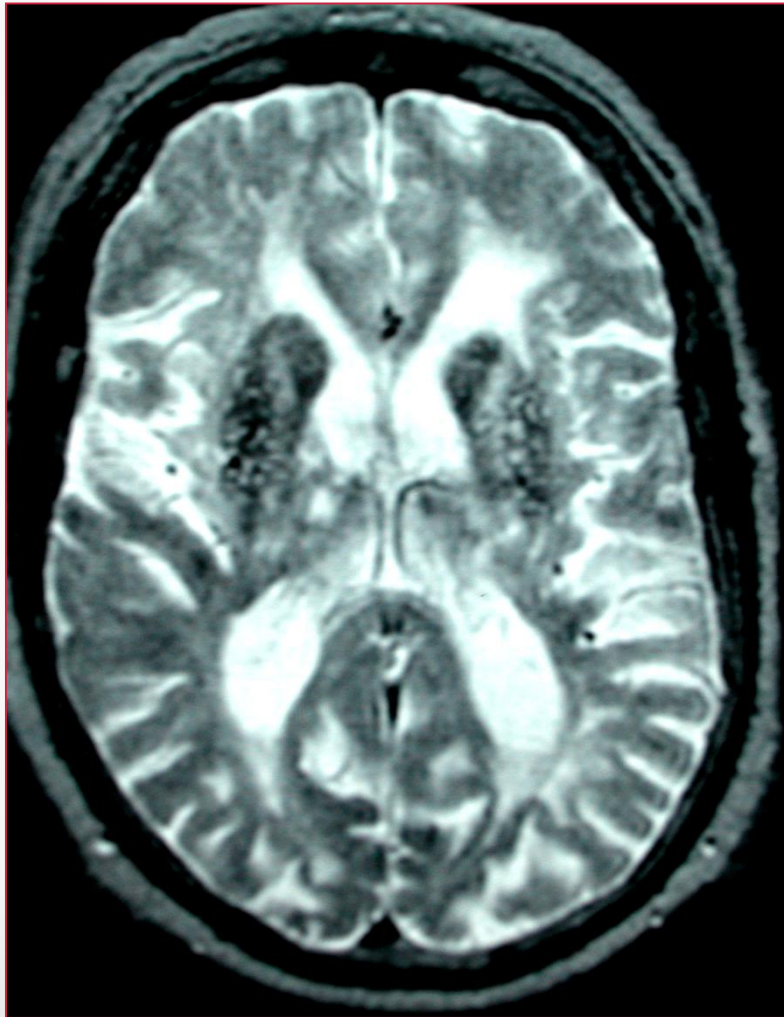


# Leukoencephalopathy



# Status Cribrosus

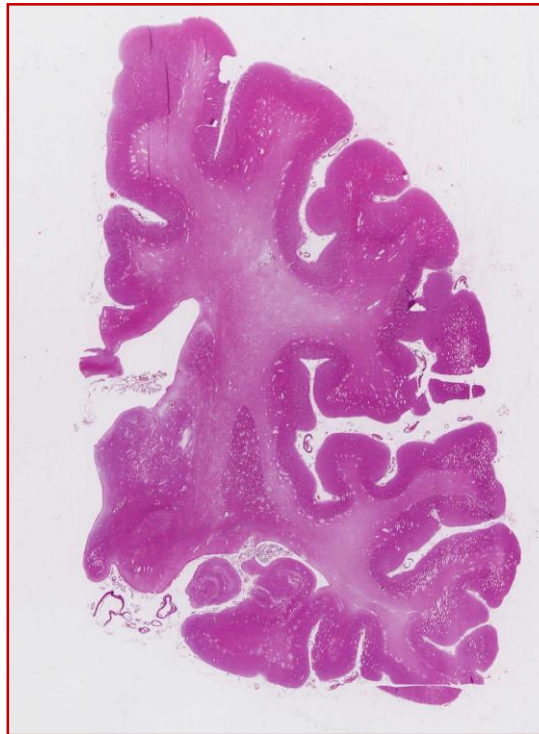
## in Basal Ganglia and Thalamus



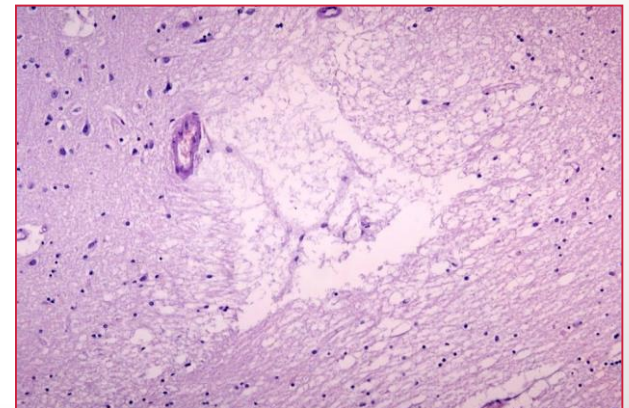
# Status Cribrosus at the Cortico-subcortical Junction



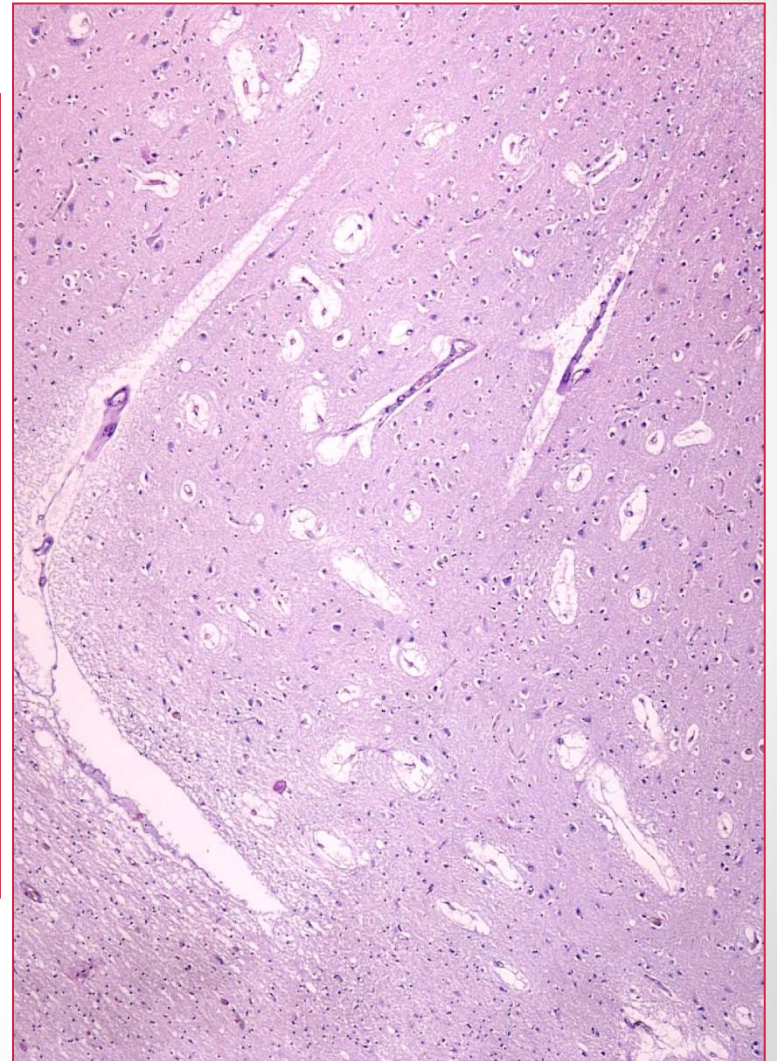
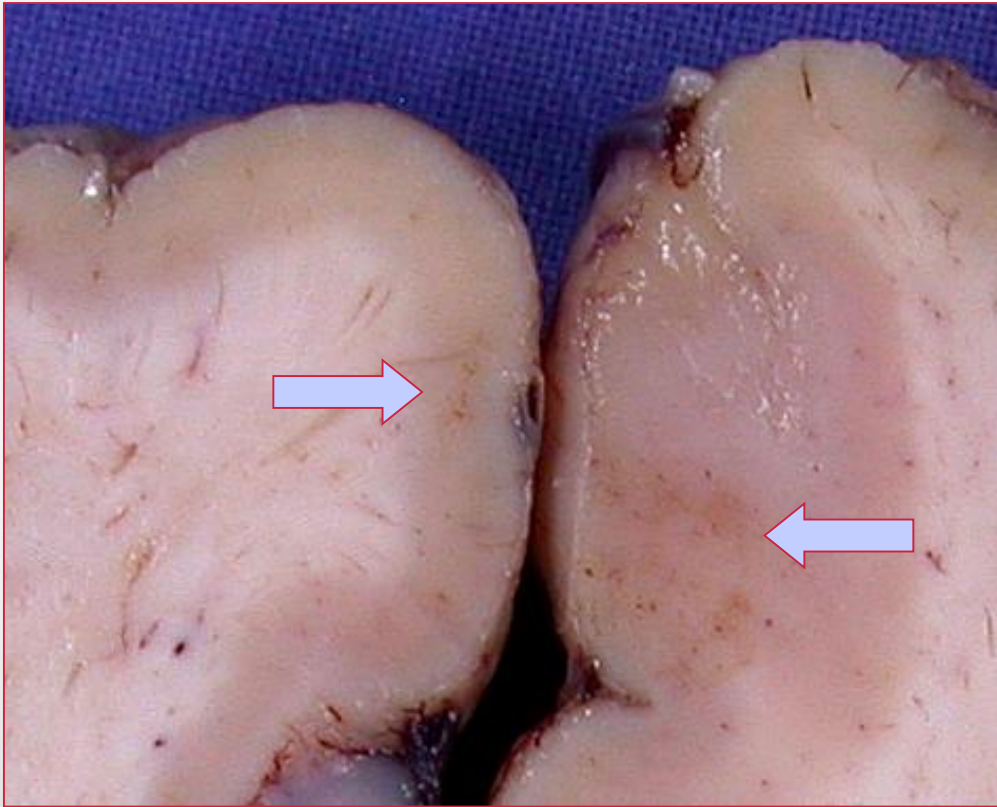
“Subcortical lacunar lesions”  
van Den Boom et al.  
*Radiology* 2002; **224**: 791-6.



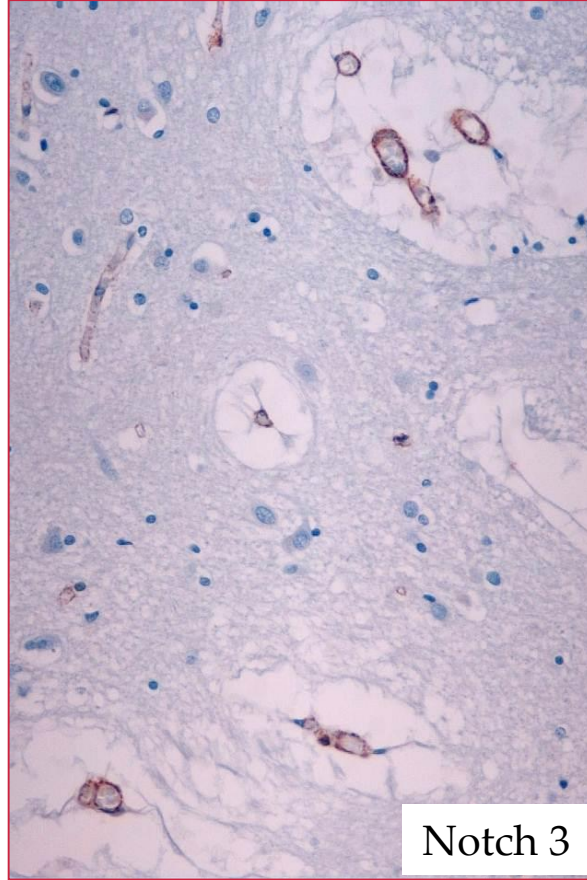
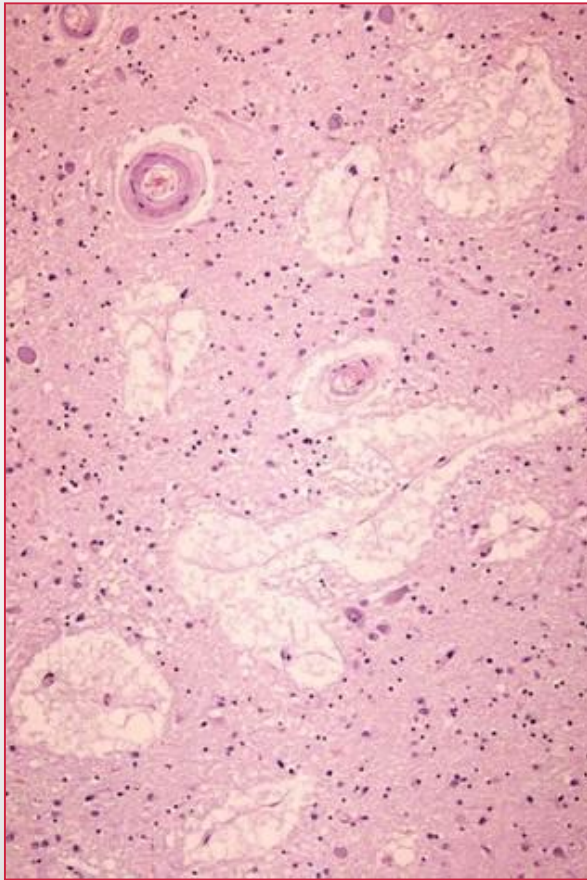
“Laminar lacunar lesions”  
Ruchoux et al.  
*Acta Neuropathol* 1995; **89**:  
500-12



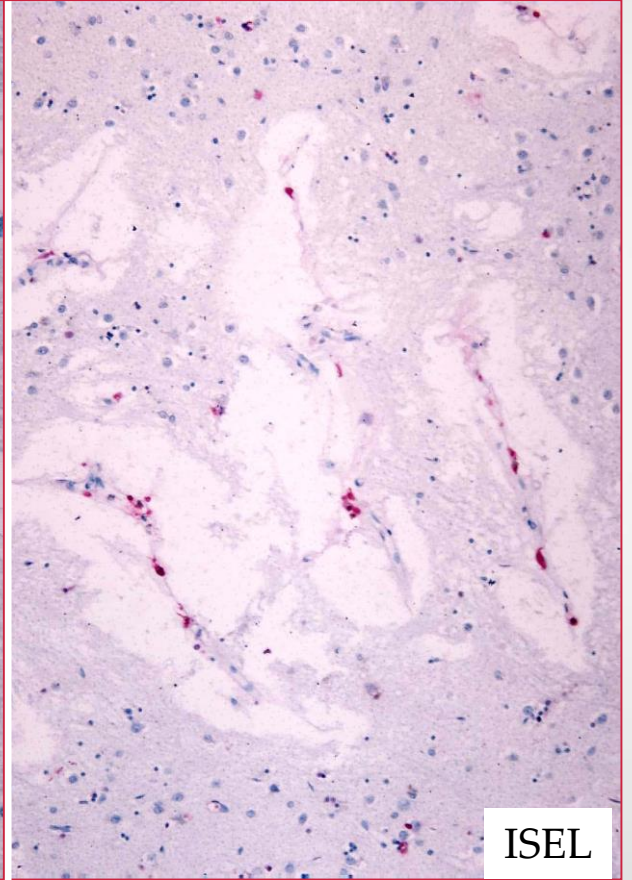
# Status Cribrosus within the Cerebral Cortex



# Status Cribrosus in CADASIL



Notch 3



ISEL

# Status Cribrosus in CADASIL

(Gray *et al.* *J Neuropath Exp Neurol* 2007; 66: 597-607)

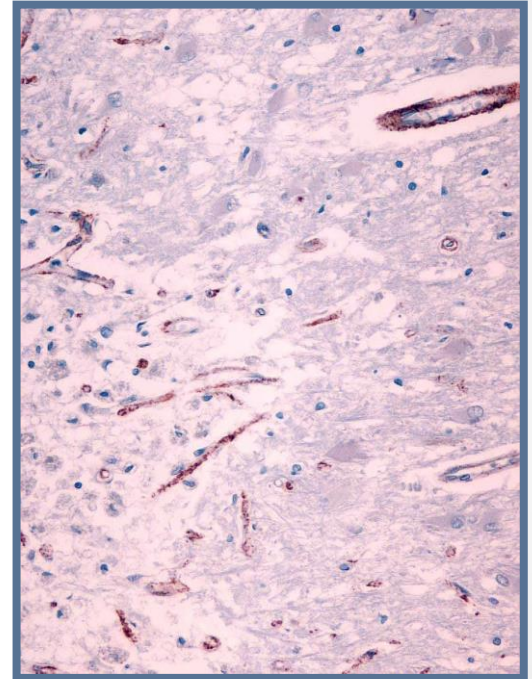
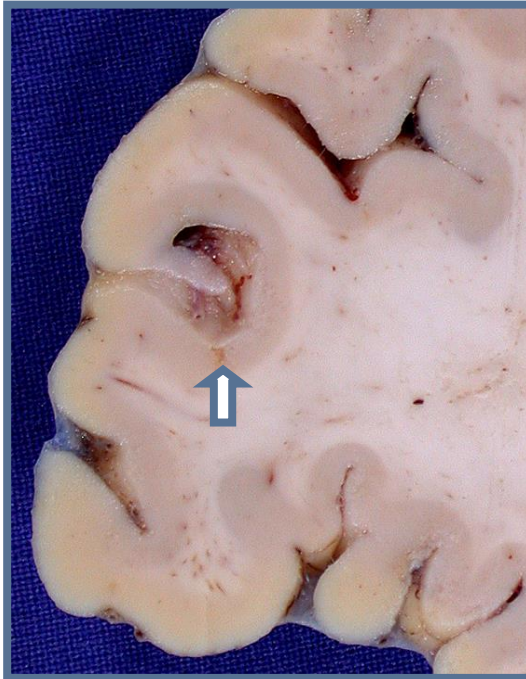
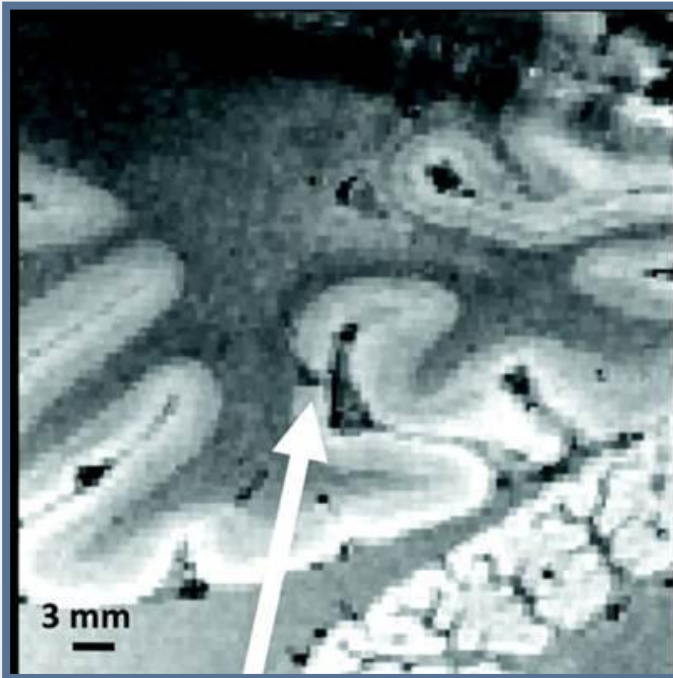
- Apoptosis of endothelial cells is markedly increased in brain regions showing status cribrosus in CADASIL
- This suggests that together with ECDN3 deposits, it could play a role in the alteration of BBB responsible for status cribrosus which is a specific change in CADASIL

# Involvement of the Cerebral Cortex in CADASIL

Considered uncommon

- Status cribrosus within the cerebral cortex
- Cortical micro infarcts
- Cortical atrophy associated with neuronal apoptosis

# Cortical Micro-Infarcts



Combined 7-Tesla MRI

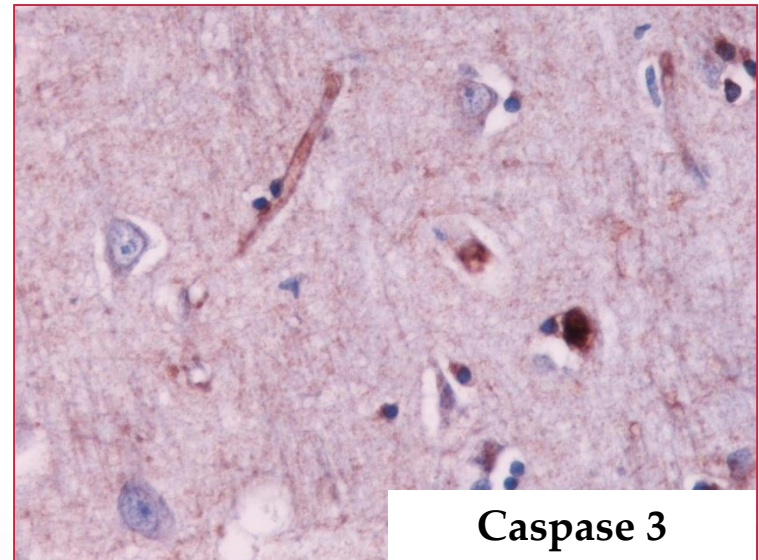
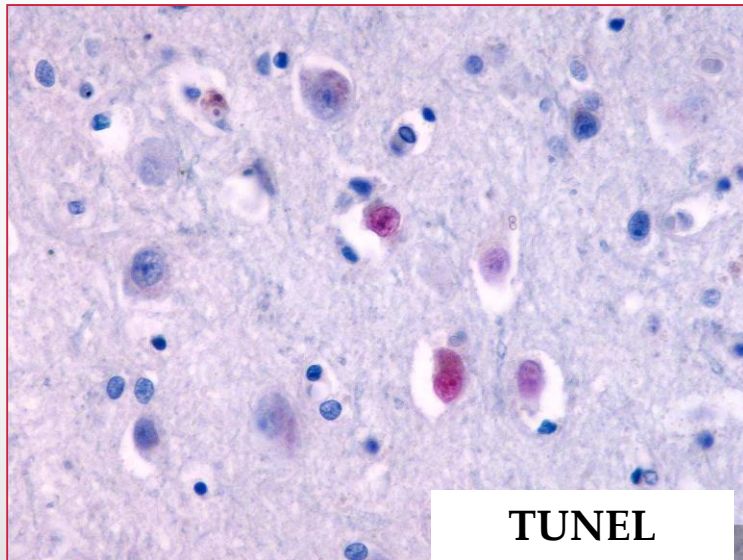
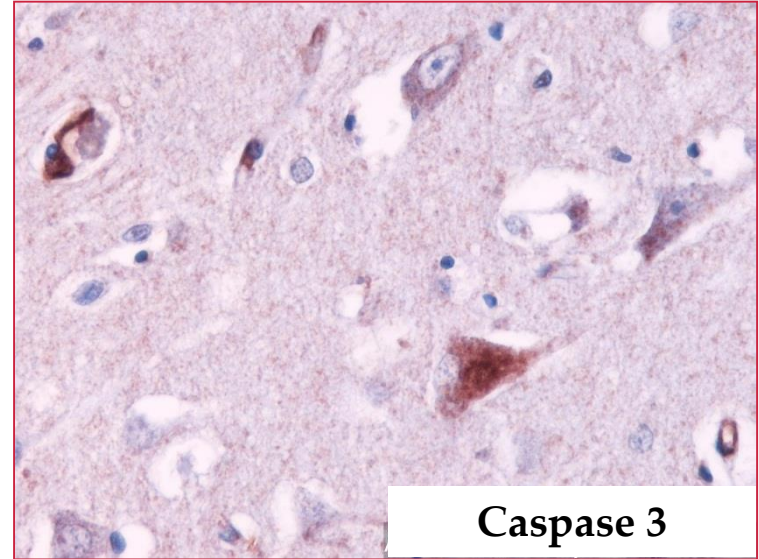
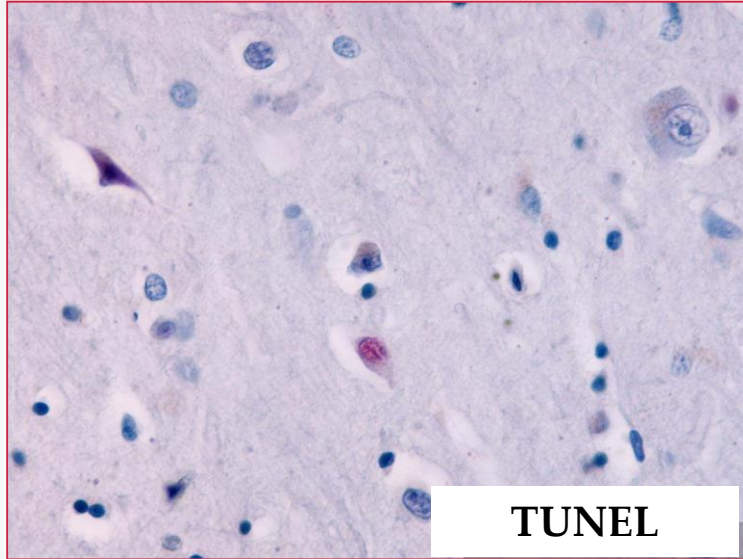
(Jouvent et al. *Stroke* 2011; 42: e27-30)

# Cortical Neuronal Apoptosis in CADASIL

(Viswanathan *et al. Stroke* 2006; 37: 2690-5)

- CADASIL is considered the archetype of pure vascular subcortical dementia
- However, MRI studies showed that cognitive decline in affected patient is associated with cortical atrophy [Peters *et al. , Neurology.* 2006;66:1517-22].
- Using ISEL and Caspase 3 IHC, we identified apoptotic neurons in the cerebral cortex of patients with CADASIL

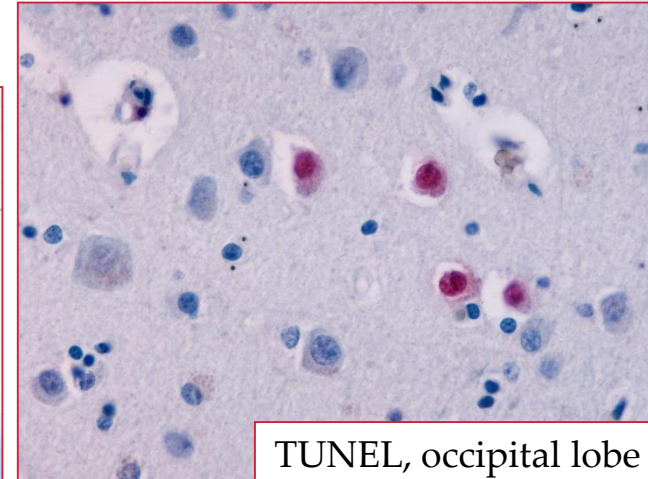
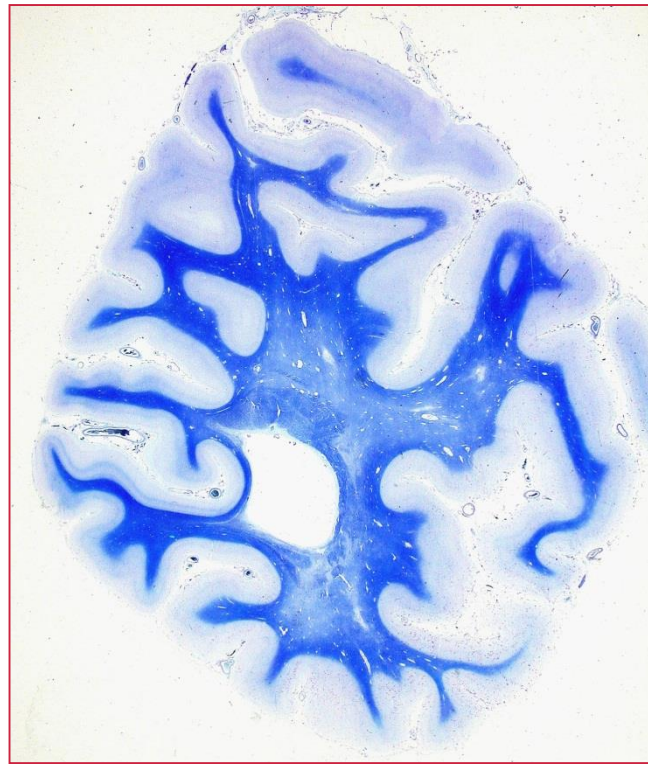
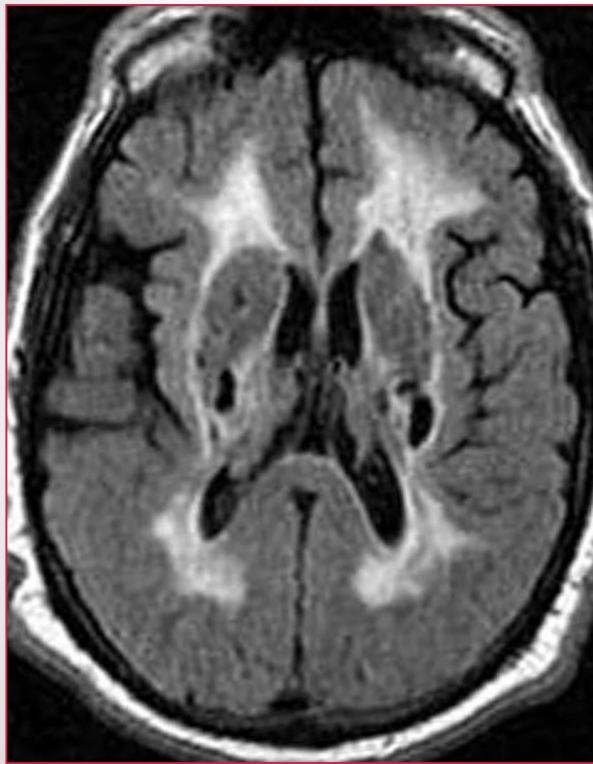
# Cortical Neuronal Apoptosis



# Cortical Neuronal Apoptosis in CADASIL

- Predominates in layers 3-5
- No topographical correlation with the rare cerebral micro-infarcts
- Close topographical relationships with axonal changes in the subcortical white matter
- Intensity well correlated with that of the cognitive disorders

# Cortical Neuronal Apoptosis



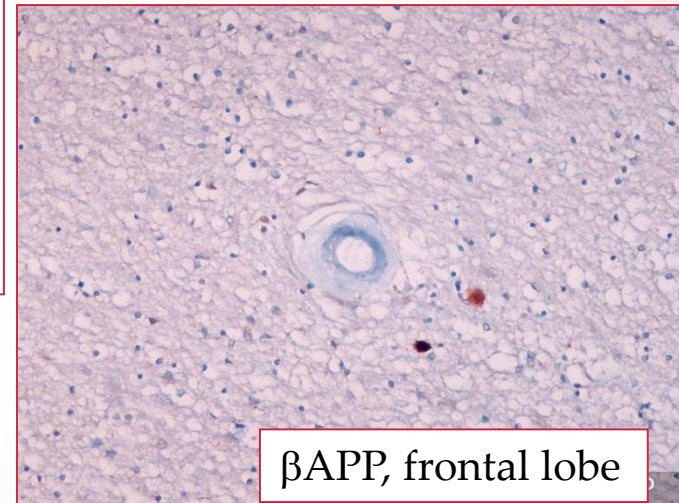
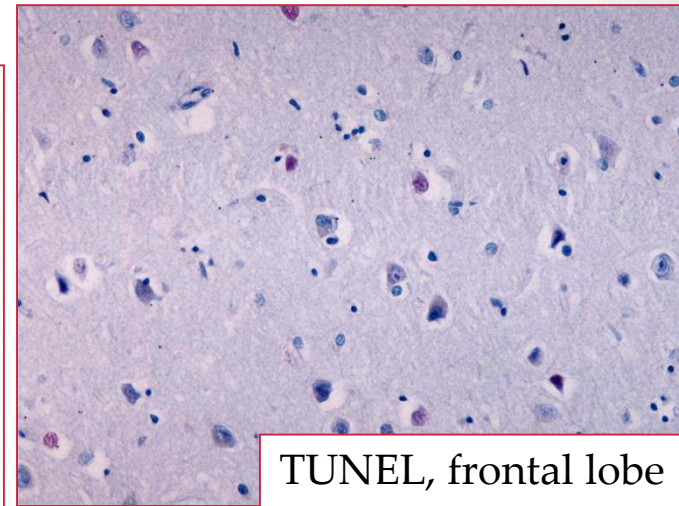
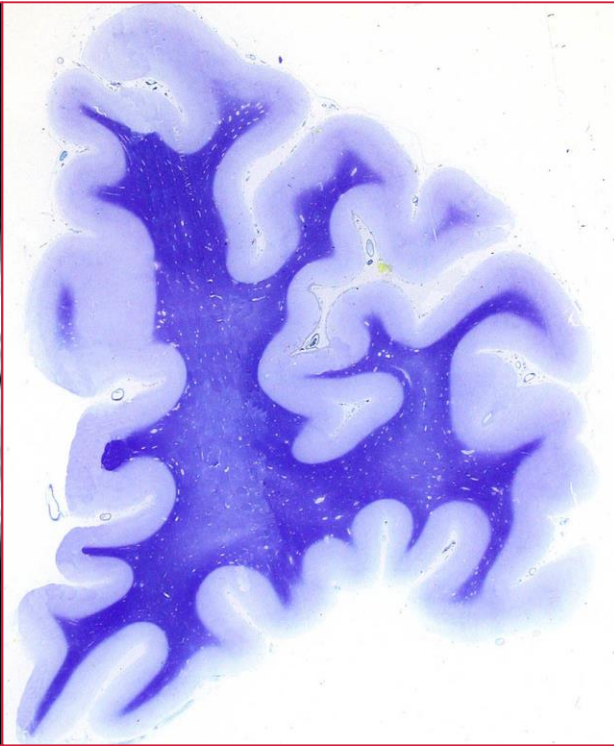
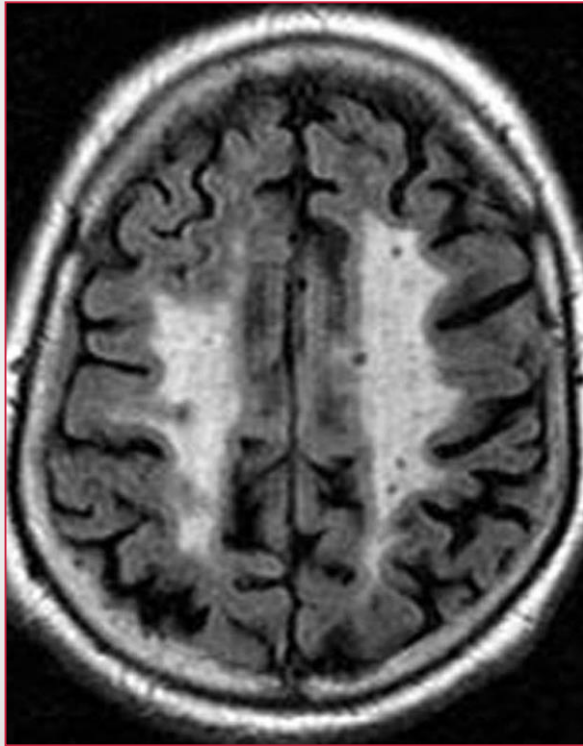
TUNEL, occipital lobe



βAPP, occipital lobe

Patient with severe dementia

# Cortical Neuronal Apoptosis



Patient with MMS 20 just before death

# Cortical Neuronal Apoptosis in CADASIL

(Viswanathan *et al. Stroke* 2006; 37: 2690-5)

- Cortical neuronal apoptosis in CADASIL does not seem to be the consequence of ischemic vascular changes.
- It seems more likely **secondary to axonal changes** in the underlying subcortical WM, via axonal retrograde degeneration or deafferentation.

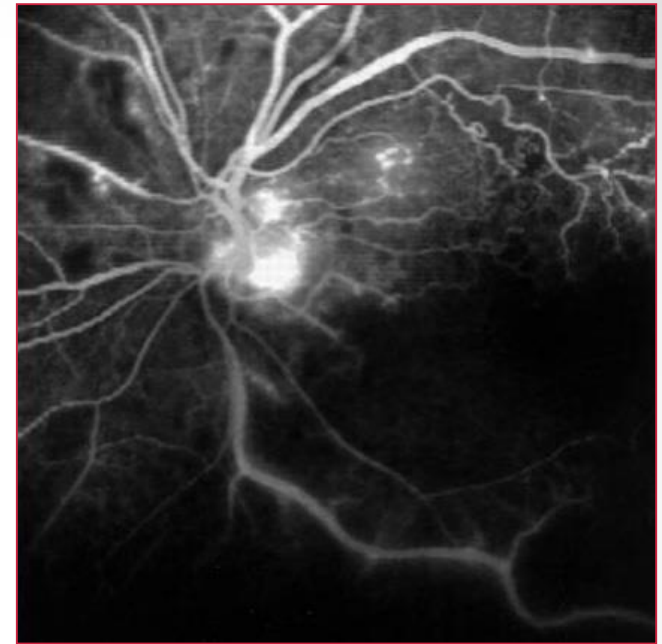
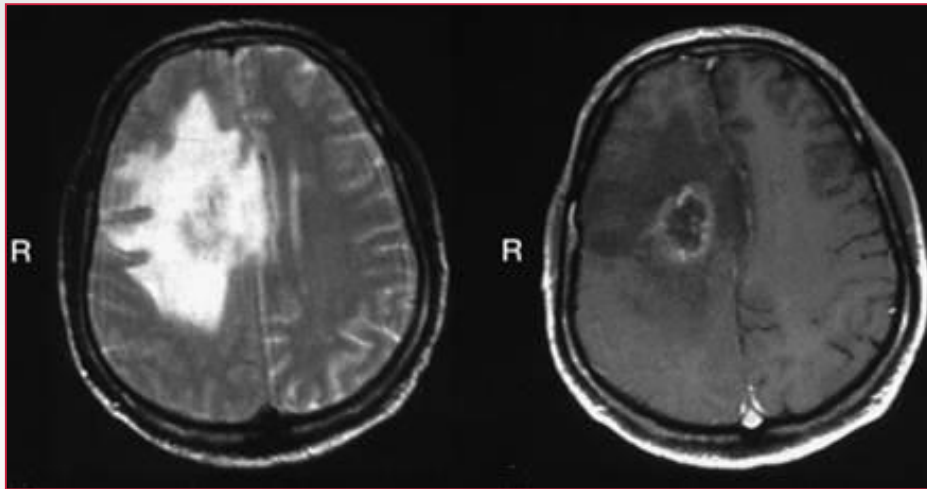
# **Hereditary small vessel diseases of the brain and/or retina:**

## **Retinal vasculopathy with cerebral leukodystrophy (RVCL)**

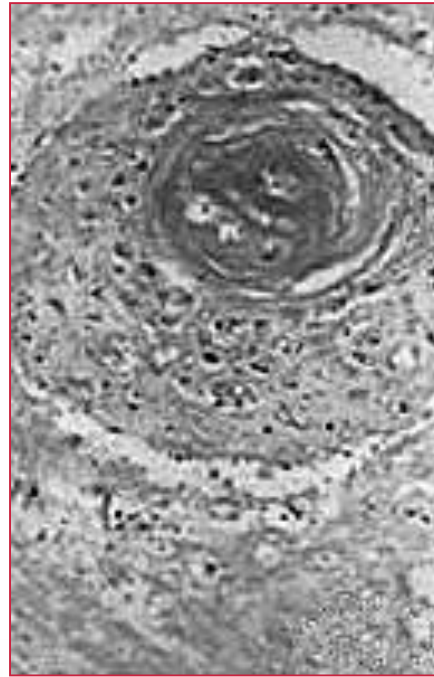
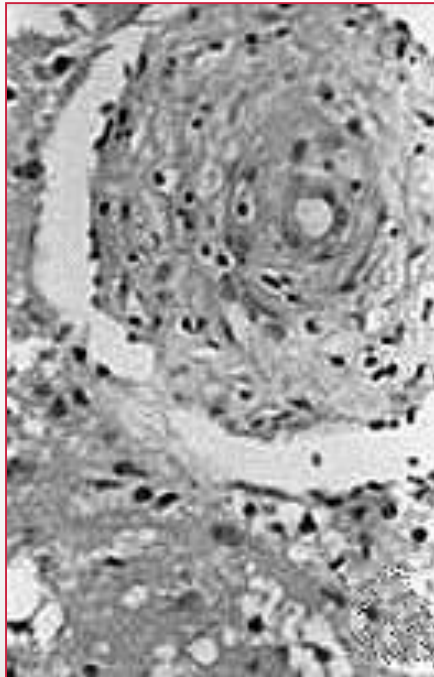
# Hereditary small vessel diseases of the brain and/or retina

## Neuropathological data

- Predominant involvement of the deep white matter and basal ganglia
- Cerebral microvascular alterations: fibrous thickening of the vessel wall and sometimes fibrinoid necrosis and thrombosis
- Distinctive multilaminated vascular basement membranes in the brain, kidney, stomach, appendix, omentum, and skin on E.M.



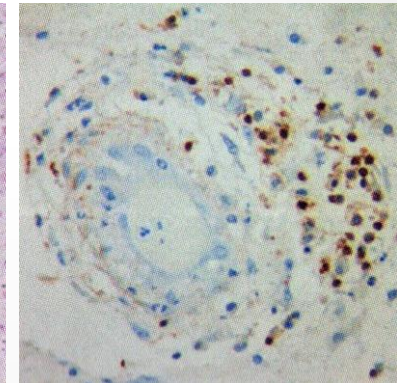
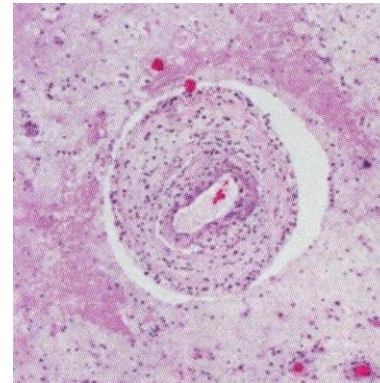
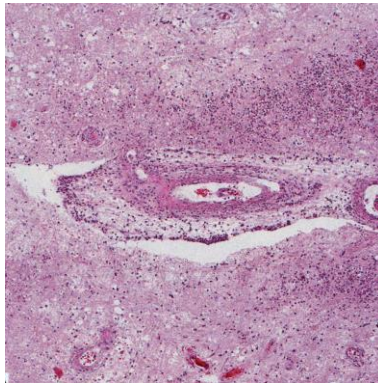
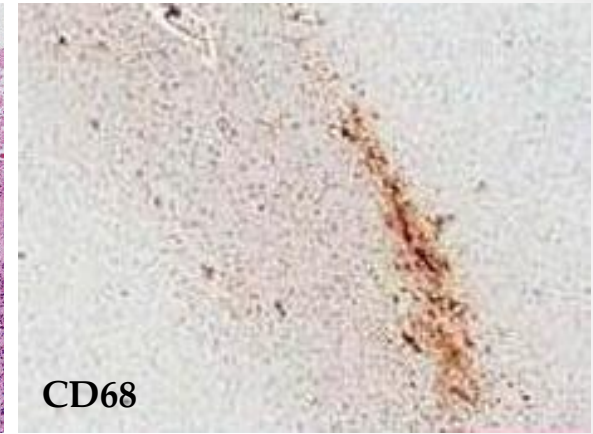
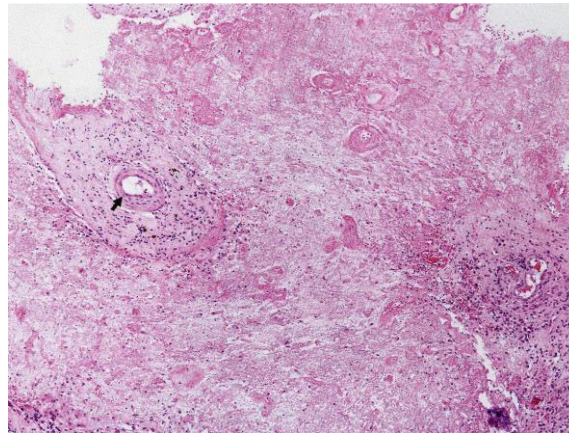
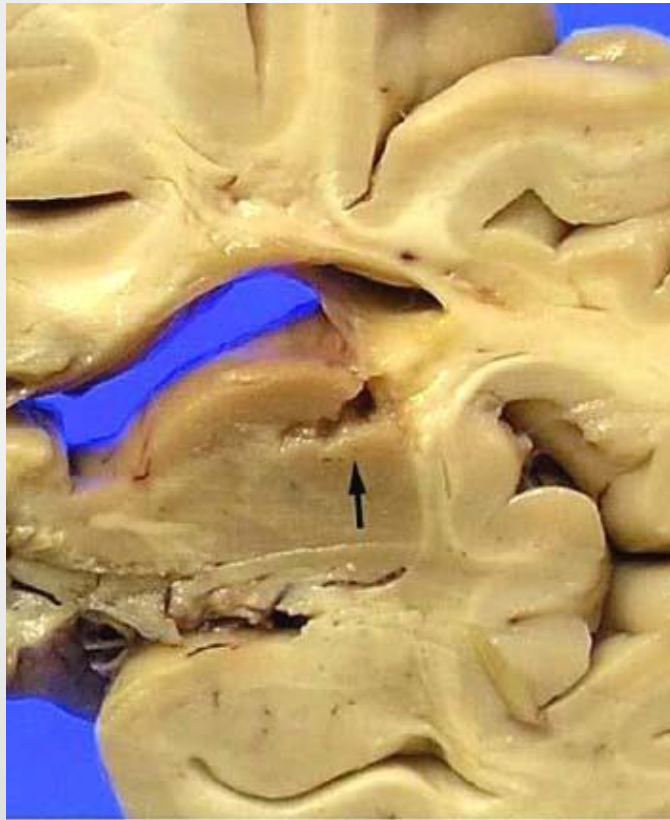
Macular edema with capillary  
dropout and perifoveal  
microangiopathic  
telangiectases



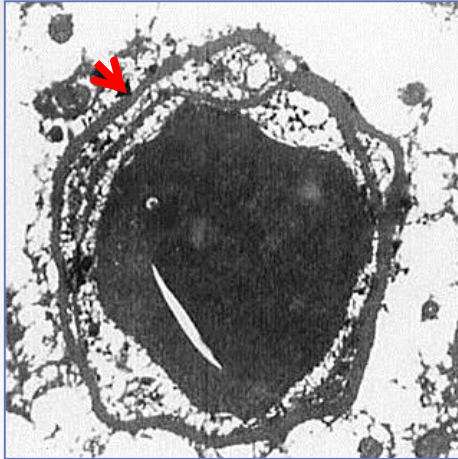
Fibrous thickening of vessel walls  
Necrosis and thrombosis of the vessel

**Cerebroretinal vasculopathy**  
Weil et al, Neurology, 1999

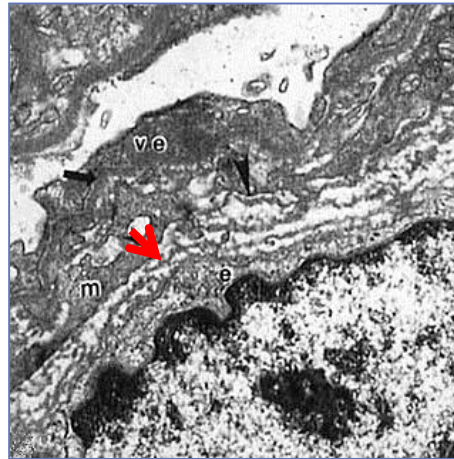
# Hereditary small vessel diseases of the brain and/or retina



*Kolar GR et al. Brain Pathology 2014; 24: 510-18*



Brain capillary



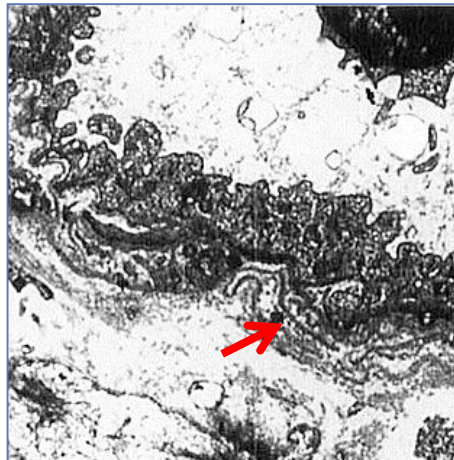
Glomerular capillary wall



Renal peritubular capillary



Cutaneous vessel



Gastric mucosa

**Multilaminated basement membranes in various organs at ultrastructural study**

*Jen et al.*  
*Neurology 1997;49:1322-30*

**Small Vessel Diseases  
associated with  
*COL 4A1* & *COL 4A2*  
mutations**

# *COL4A1 & COL4A2 mutations*

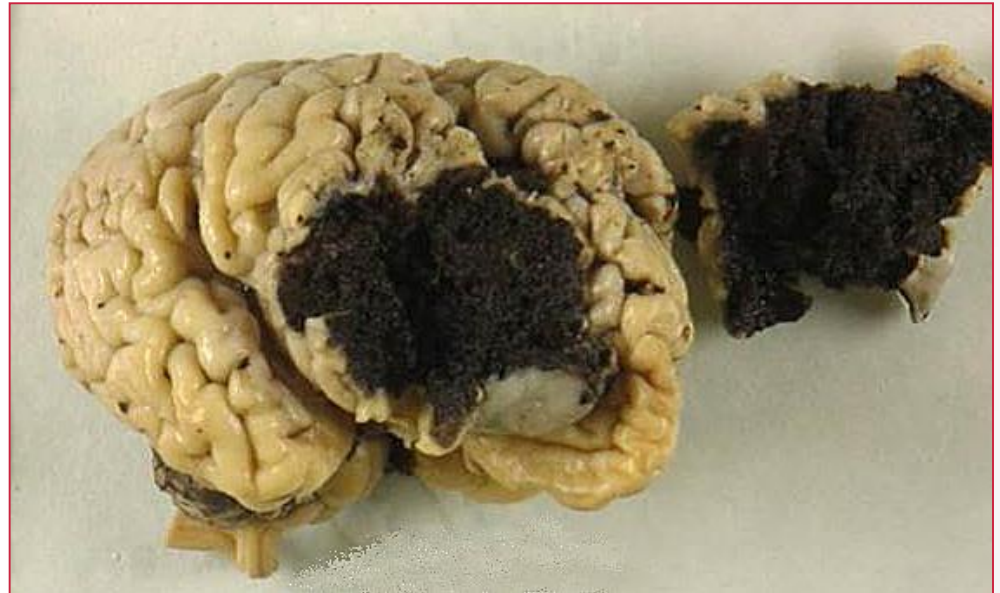
## **Changes in fetuses**

The clinical and radiological observation that brain changes involve mainly children or young adults suggests that the lesions might be antenatal.

COL 4A1 mutation was found in 2 fetuses with porencephaly leading to VIP

(J. Tran Van Nhieu & F. Encha Razavi personal communication)

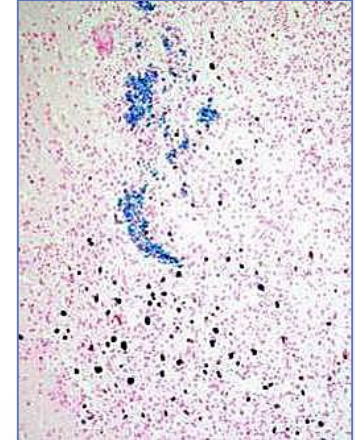
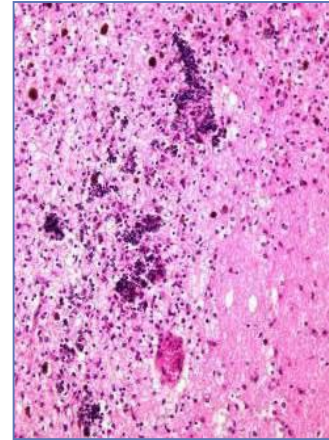
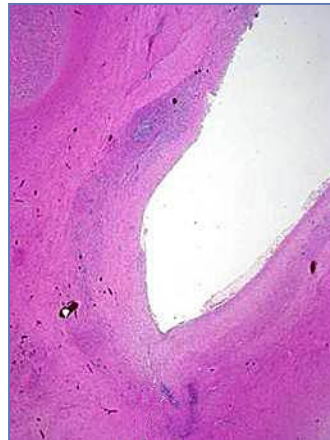
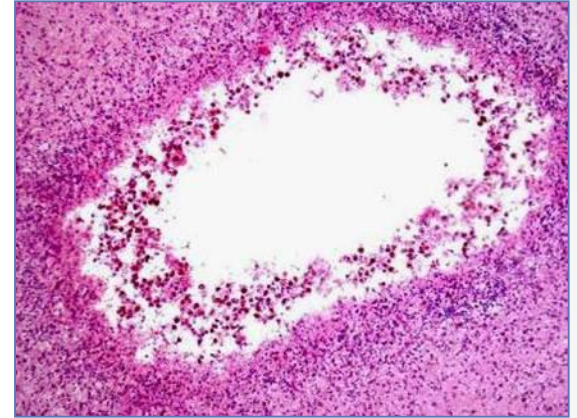
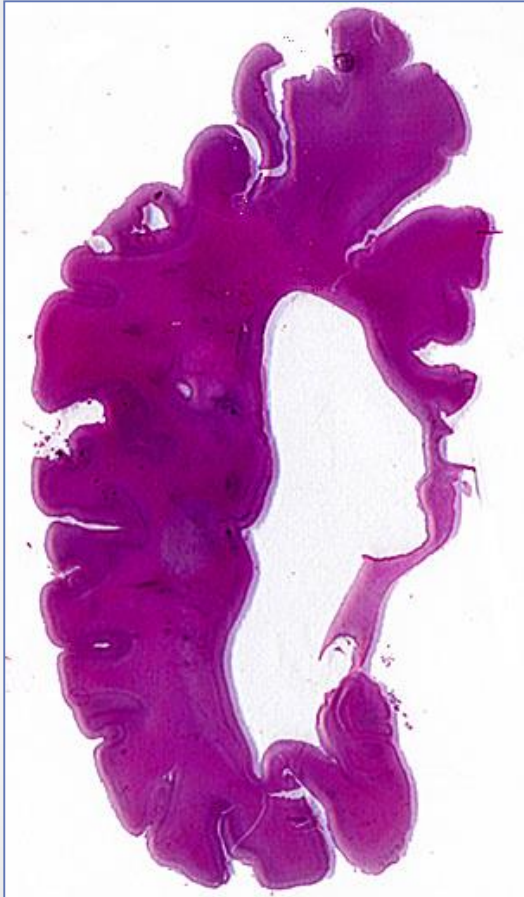
# *COL4A1* mutation in the foetus



**Recent Hemorrhage**

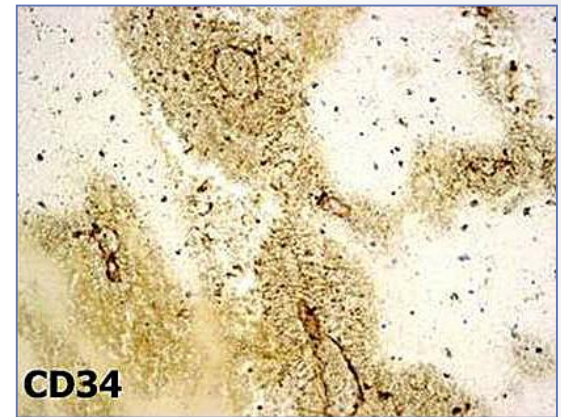
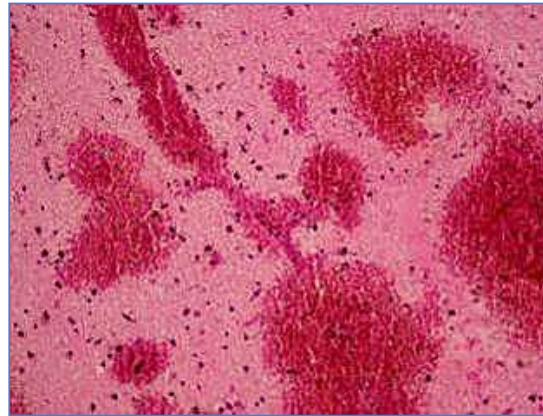
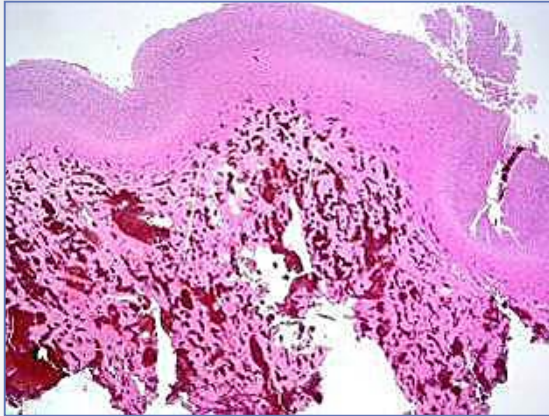
Ventricular Dilatation  
Cavitory necrotic lesion (Porencephaly)  
Old hemorrhage

# *COL4A1* mutation in the foetus

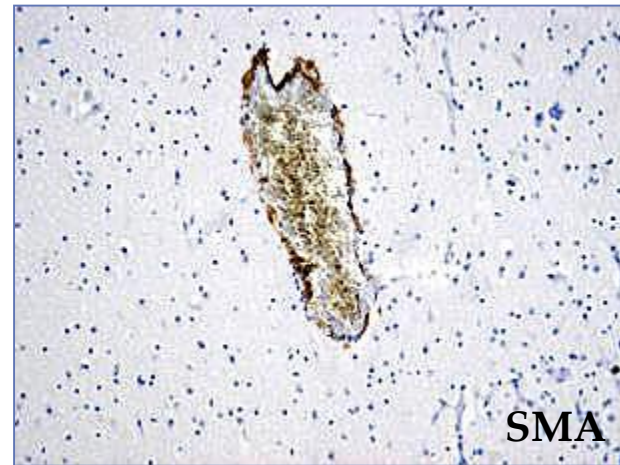
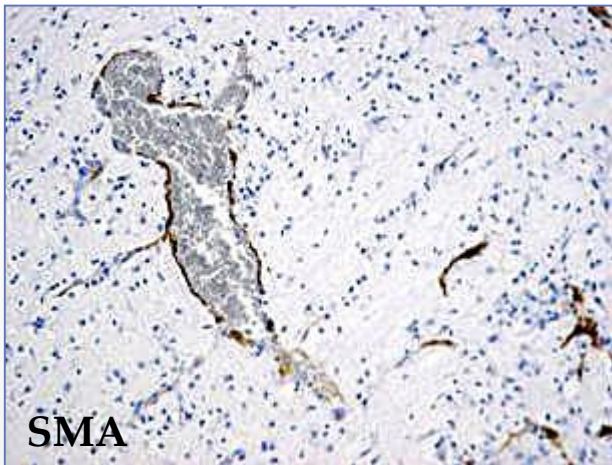


Cavitory necrotic lesion (Porencephaly)  
Old hemorrhage

# *COL IVA1* mutation in the foetus



Persistence of normal vessels within petechiae (vascular fragility?)

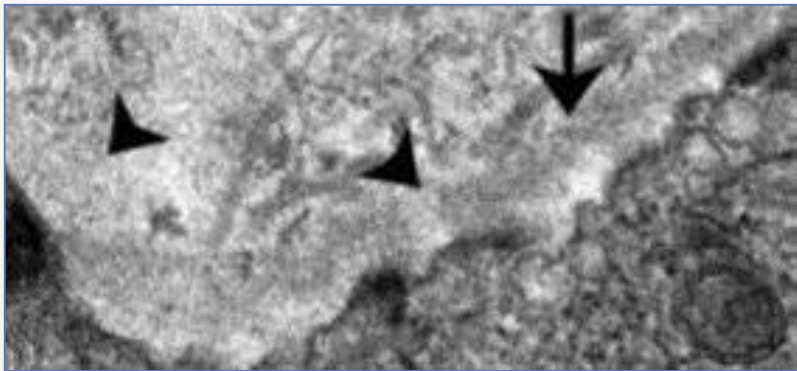


Irregularity of the smooth muscle layer which is fragmented or thickened

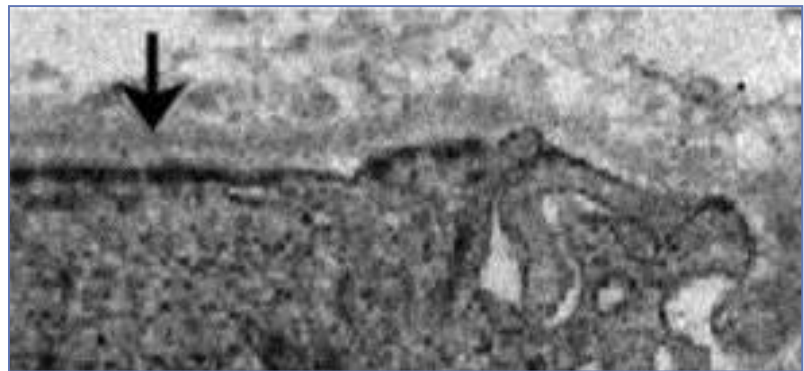
# *COL4A1* & *COL4A2* mutations in adults

Vascular changes on skin biopsies:

By E.M. : basal membrane defects in affected individuals compared to controls



Patient



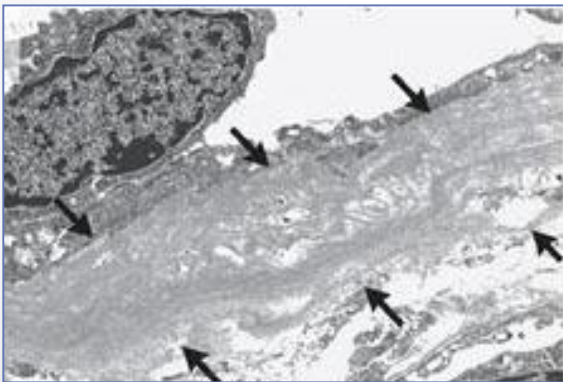
Control

(Murray et al. *Human Molecular Genetics* 2014;23:283-92)

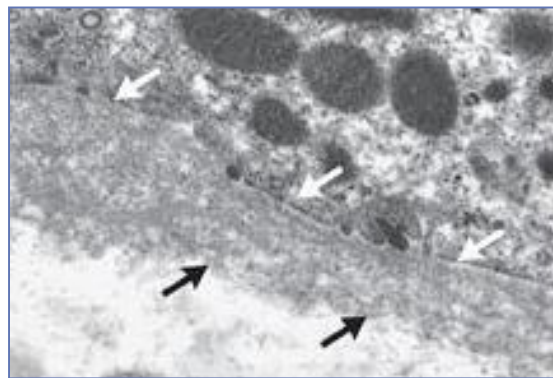
# *COL4A1 & COL4A2* mutations in adults

## Vascular changes on renal biopsy:

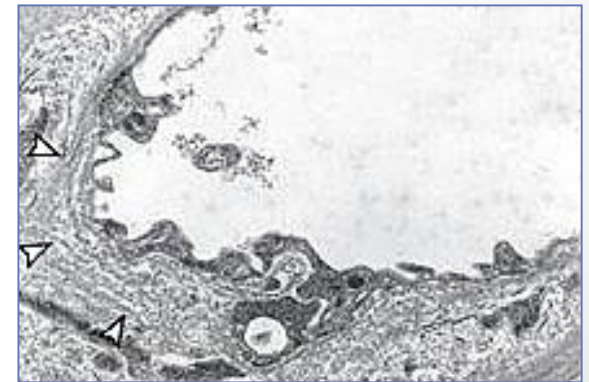
- By E.M. : thickening and splitting of the basement membrane with multiple laminations (reminiscent of HERNS) of the tubules, Bowman's capsule and interstitial capillaries



Bowman's capsule



Tubule



Interstitial capillary

(Plaisier et al. *N Engl J Med* 2007;357:2687-95)

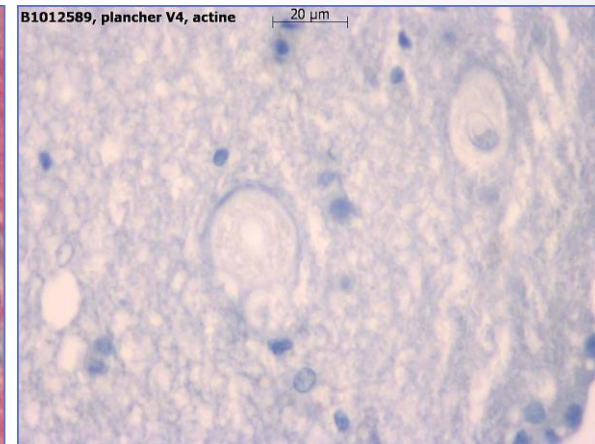
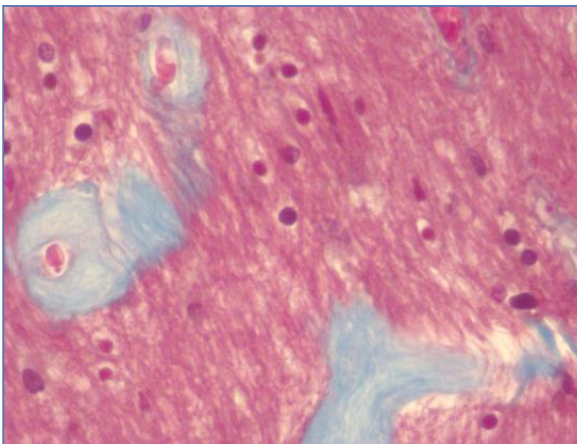
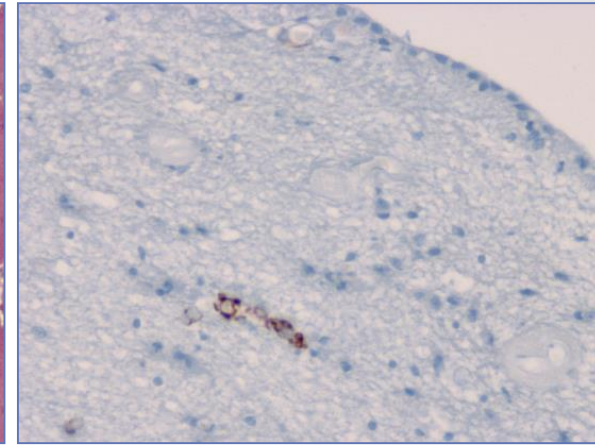
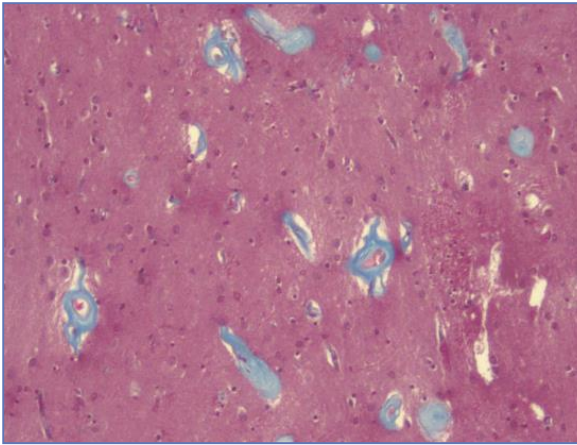
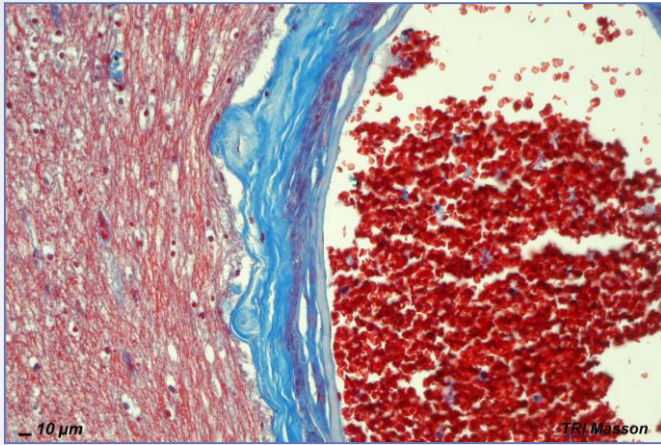
**Hereditary Extensive  
Vascular  
Leukoencephalopathy  
mapping to  
chromosome 20q13**

# HEVL mapping to chromosome 20q13

(Hervé *et al. Neurology* 2012;79:2283-7)

- **Involvement of small terminal arterioles and *vasa vasorum***
- **Topography:**
  - White matter of the cerebral hemispheres and brainstem
    - ✓ More severe in the cortico-subcortical areas
    - ✓ and in the subependymal regions
  - Basal Ganglia

# SVD mapping to chromosome 20q13



White matter

Basal ganglia

Subependymal regions

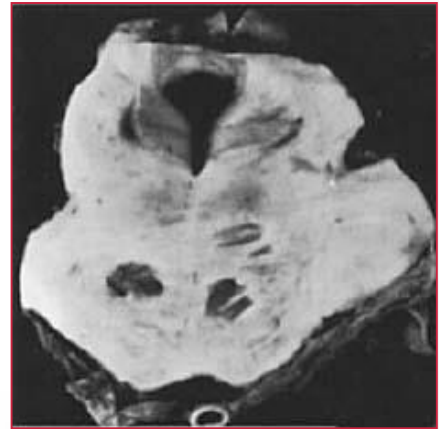
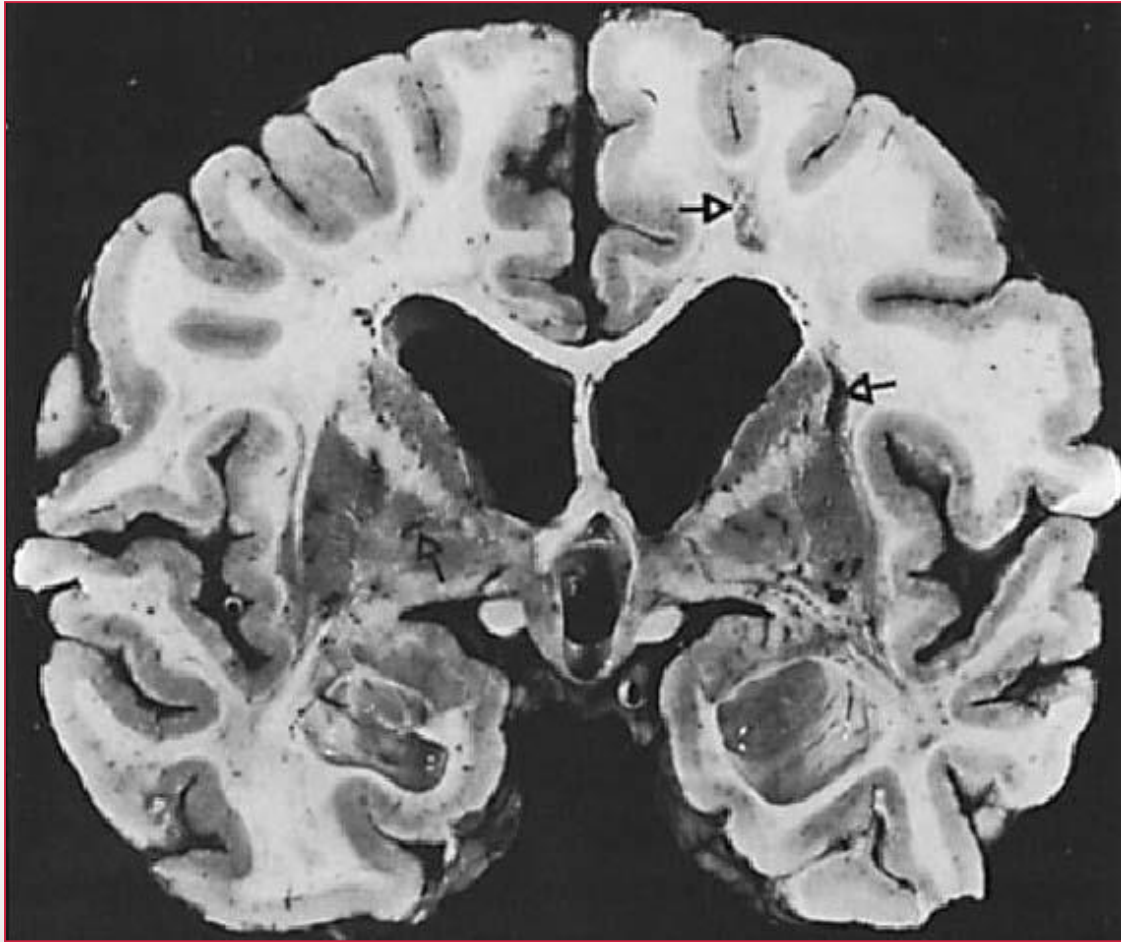
**Swedish hereditary  
multi-infarct dementia  
(Swe-hMID)**

# Swe-hMID

## Swedish hereditary multi-infarct dementia

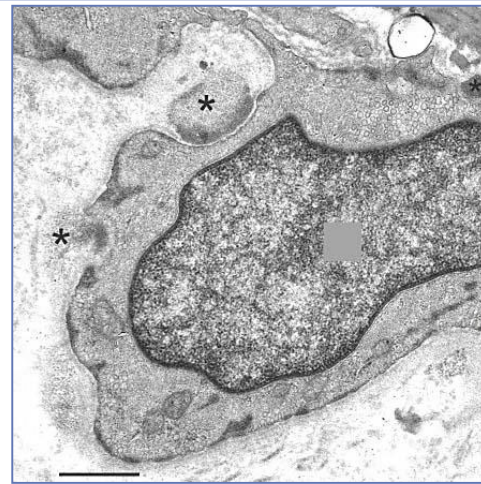
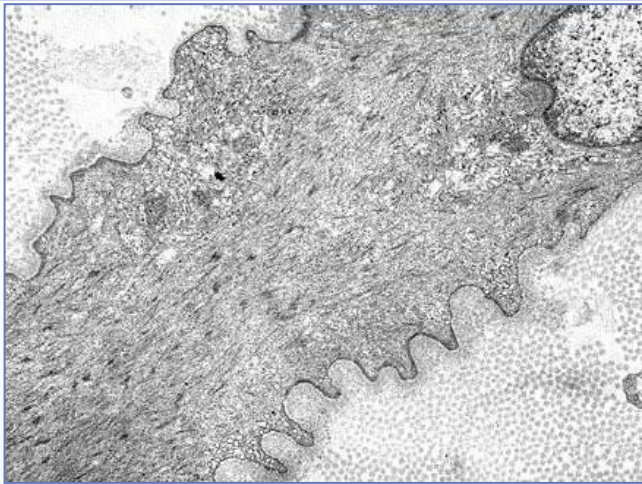
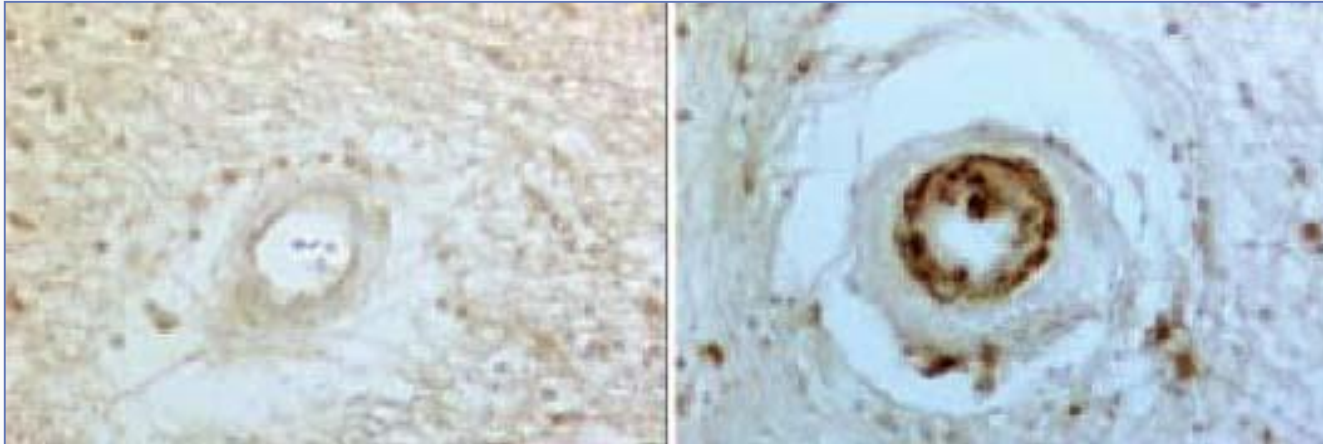
- Hereditary multi-infarct dementia in a Swedish family (Sourander & Walinder, 1977)  
No mutation of the Notch3 gene
- Chronic familial vascular encephalopathy in an English family (Stevens et al. 1977)  
R141C mutation in the Notch3 gene

# Swe-hMID



# Swe-hMID

No Notch 3 immunopositivity, no GOM,



**Swe-hMID**

**CADASIL**

Courtesy Pr. Hannu KALIMO

**Pontine Autosomal  
Dominant  
Microangiopathy &  
Leukoencephalopathy  
(PADMAL)**

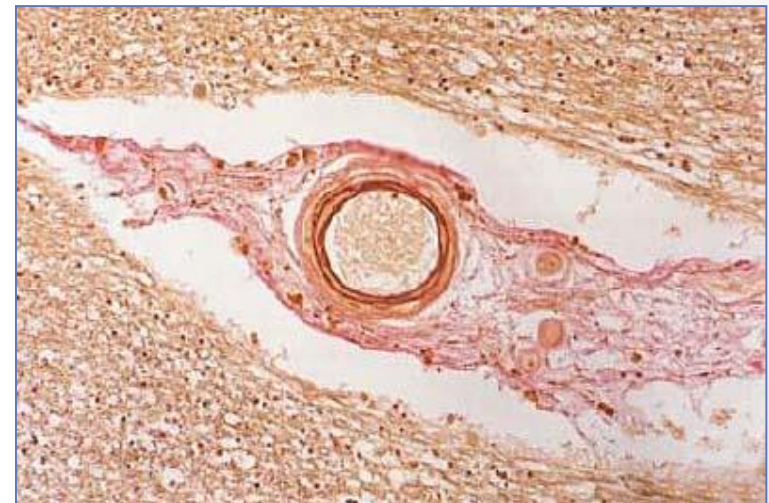
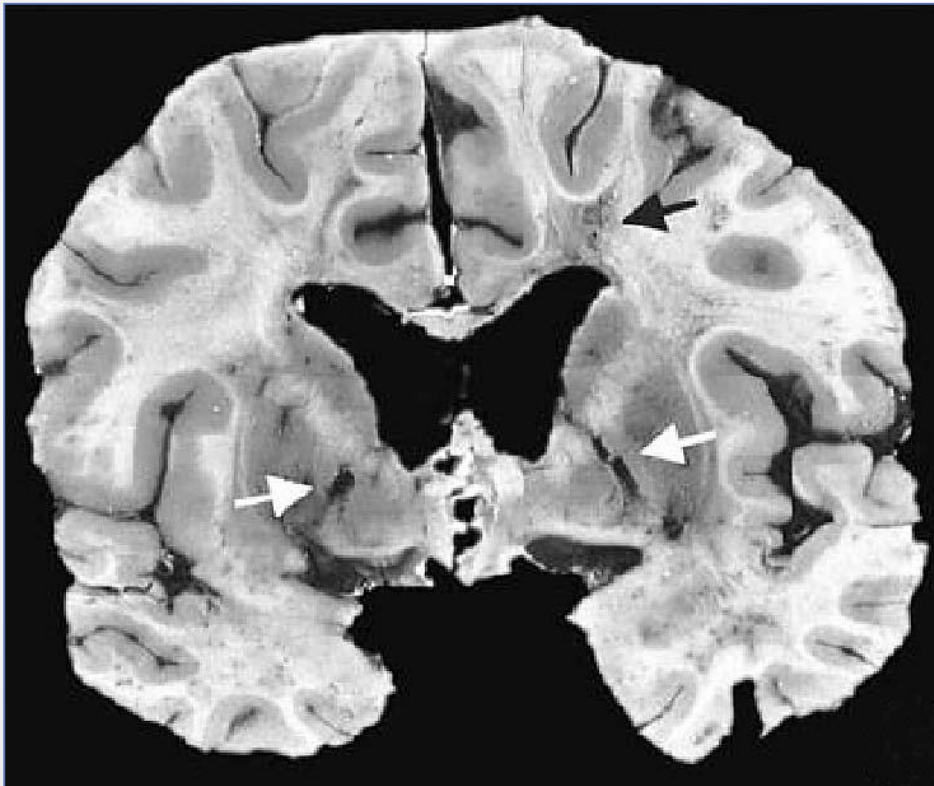
# PADMAL

(Hagel et al. Acta Neuropathologica 2004)

- Involvement of the pons +++
- Concentric intimal proliferation with hyperelastosis and atrophy of the tunica media
- No GOM, no Notch 3 positive deposits

→ Similarities +++ with Swe hMID

# PADMAL



Hagel et al. Acta Neuropathologica 2004

Concentric intimal proliferation  
Hyperelastosis  
Atrophy of the tunica media

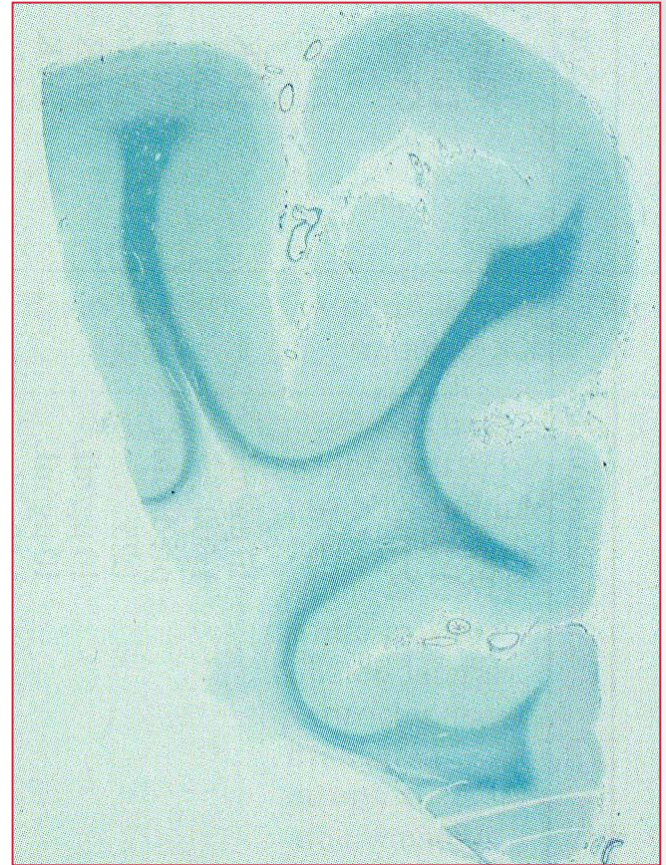
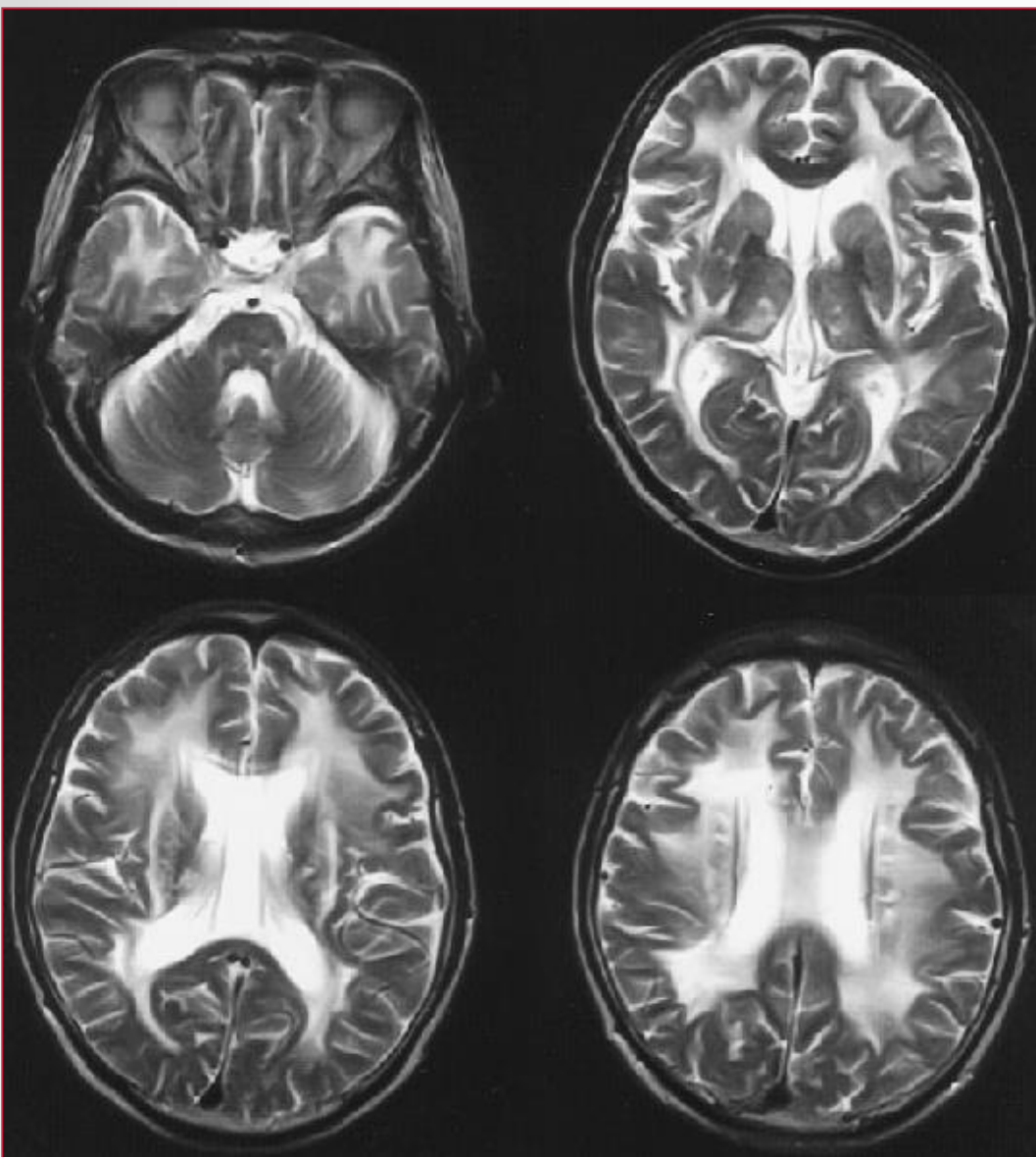
# CARASIL

Cerebral Autosomal Recessive  
Arteriopathy with Subcortical  
Infarcts & Leukoencephalopathy

Mutations of *HTRA1*

# CARASIL, Neuropathology

- Leukoencephalopathy sparing the subcortical U fibres
- Brainstem infarcts but involvement of the Basal Ganglia uncommon
- Severe atherosclerosis of the arteries of the circle of Willis



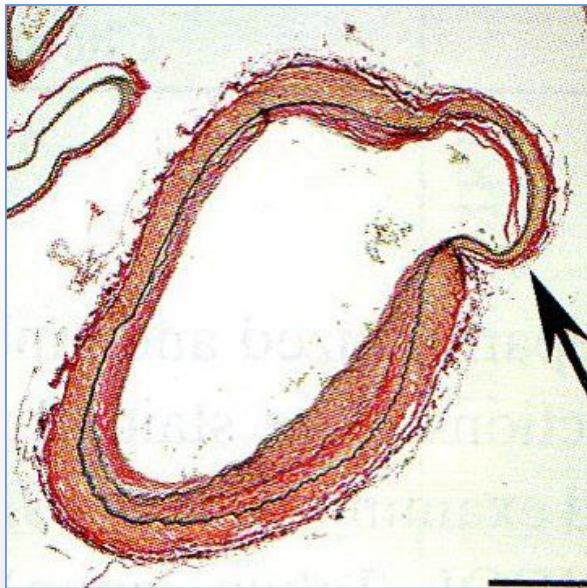
Oide *et al*,  
*Neuropathology* 2008; **28**:132-42

Yanagawa *et al*, *Neurology*, 2002, **58**: 817-820

**CARASIL**: Leukoencephalopathy sparing U fibres

# CARASIL, Neuropathology

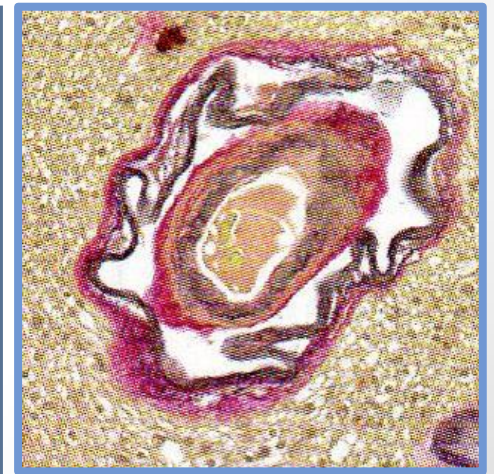
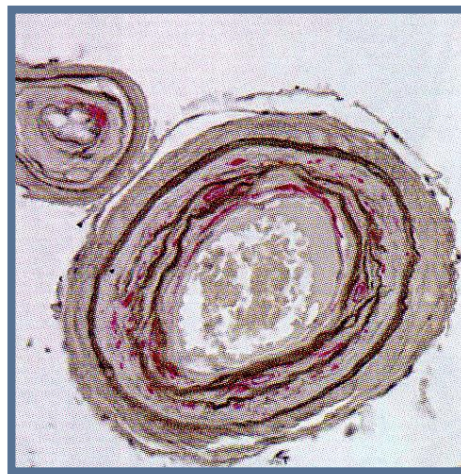
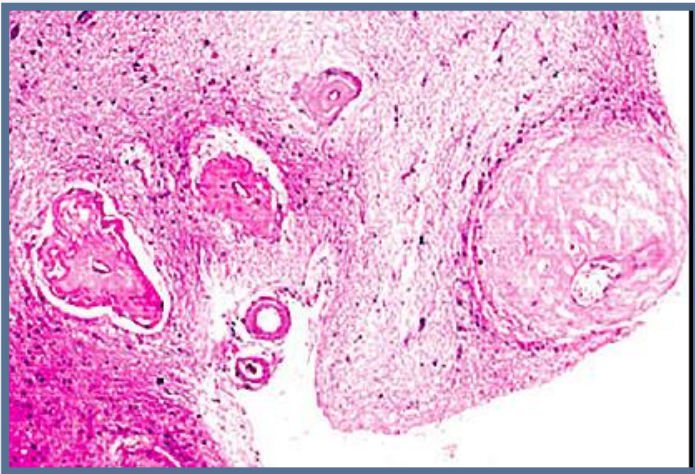
- Medial and adventitial thinning in **small and medium-sized cerebral arterioles**, sometimes with aneurysmal formation.



Oide *et al*, *Neuropathology* 2008; **28**:132-42

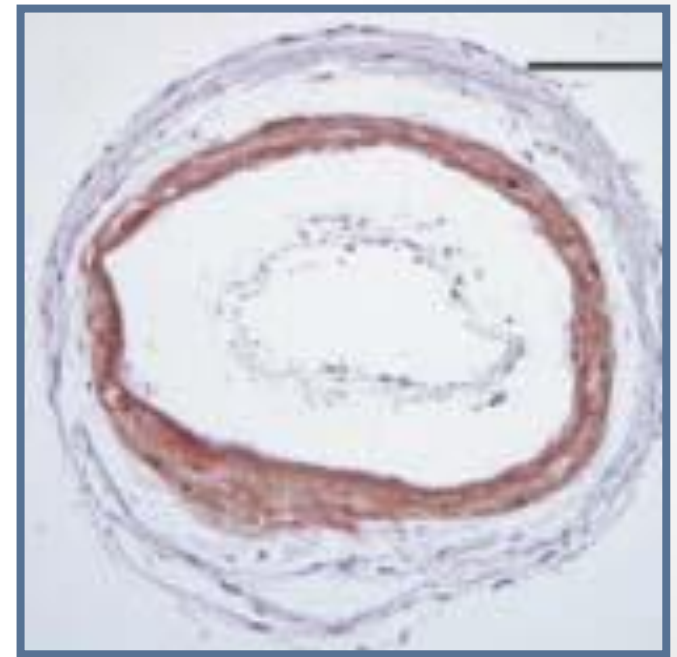
# CARASIL, Neuropathology

- Arteriolosclerosis-like changes:
  - Intimal proliferation and stenosis
  - Fibrosis and hyaline degeneration of the media with smooth muscle cell loss, splitting of the internal elastic lamina, and sometimes double barreling



# CARASIL, Neuropathology

- Experimental data suggest that CARASIL could be included in the spectrum of diseases associated with the dysregulation of TGF- $\beta$  signaling
- **Hyperexpression of TGF- $\beta$**  has been demonstrated in the media of small cerebral vessels in CARASIL patients



Hara et al. *N Engl J Med* 2009;360:1729-39.

# **Leukoencephalopathy, Cerebral Calcifications and Cysts (LCC)**

# LCC

Labrune *et al.*, *Neurology* 1996;46:1297-301

Linnankivi *et al.* *Neurology* 2006;67:1437–43

Kleinschmidt-DeMasters *et al.* *J Neuropathol Exp Neurol* 2009;68:432-439

## Radiology/Macroscopy

- Extensive brain calcifications,
- Leukodystrophy
- Formation of parenchymal cysts

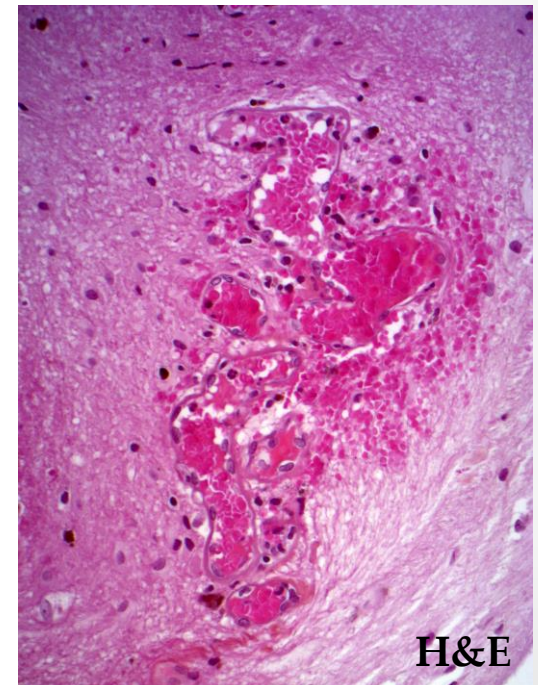
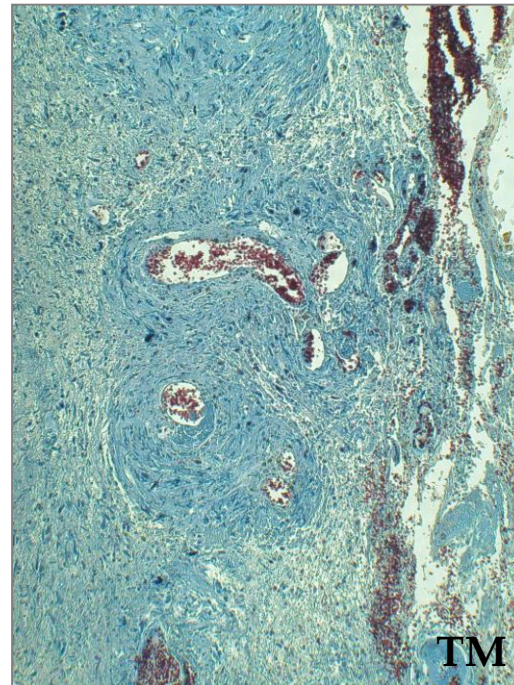
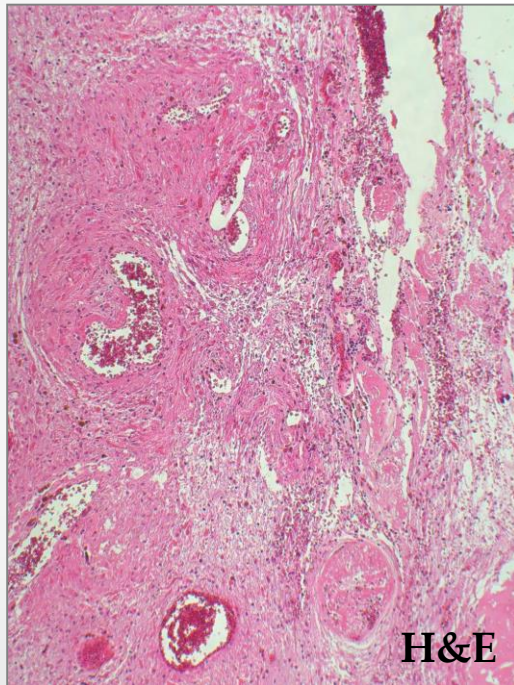
# LCC

## Pathology

- Exuberant angiomatous proliferation of abnormal small vessels +++
  - Necrosis with cysts formation
  - Gliosis +++ Rosenthal fibres
  - Microcalcifications
- } Secondary changes

# Leukoencephalopathy, Cerebral Calcifications and Cysts

Exuberant angiomatous proliferation of abnormal small vessels

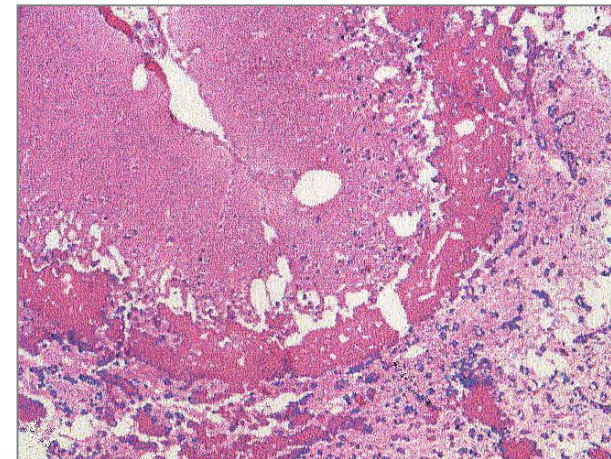
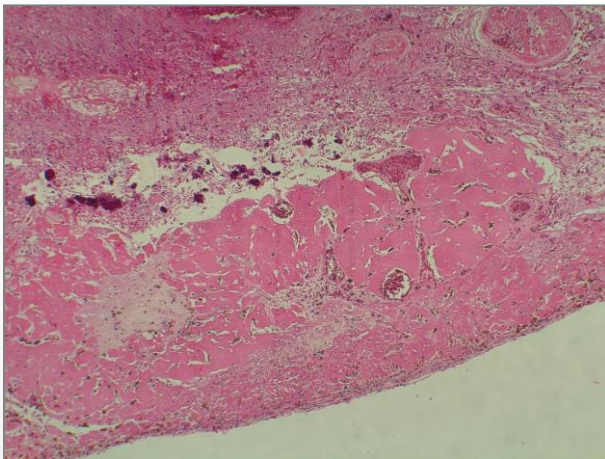
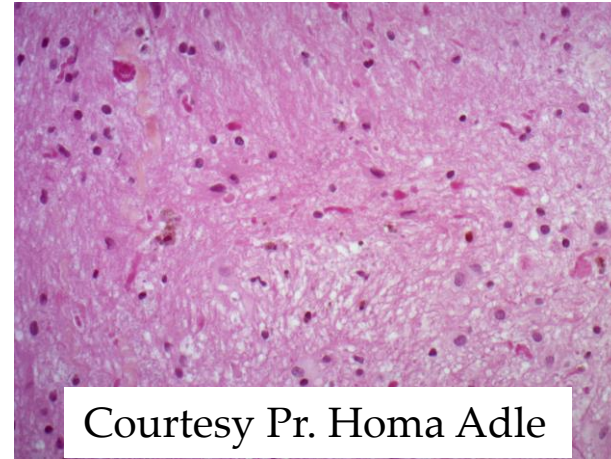
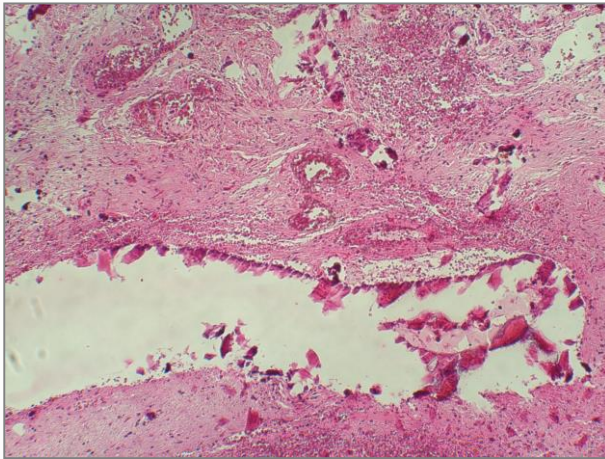


Courtesy Dr. Catherine Lacroix

Courtesy Pr. Homa Adle

# Leukoencephalopathy, Cerebral Calcifications and Cysts

Necrosis, cyst formation, calcifications and gliosis



Courtesy Dr. Catherine Lacroix

Linnankivi *et al. Neurology* 2006;67:1437-43

# Conclusion (1)

- The diagnosis of hereditary diseases of cerebral small vessels (HDCSV) is becoming an important issue in patients presenting with vascular or degenerative neurological diseases.
- Except for CADASIL which remains the prototypic HDCSV, neuropathological data are very few.
- In most cases there is variable association of lacunar infarcts , microbleeds and vascular leukoencephalopathy, the markers of CSVD.

# Conclusion (2)

- Distinctive vascular changes are observed in some diseases
- In rare instances (CADASIL, LCC), these changes are specific, even diagnostic
- In others (RVCL, SVD mapping to chromosome 20q13), the changes are suggestive of a specific disease and require genetic confirmation.

# Conclusion (3)

- Finally many of these conditions are systemic and vascular changes may be present on skin, muscle, nerve or renal biopsies.
- These systemic changes are important pathophysiologically.
- However, except for CADASIL, at present these changes are not specific enough to be diagnostic.

# Thank you for your attention

**Homa ADLE-BIASSETTE**

**Marielle BAUDRIMONT**

**Catherine LACROIX**

**Jacqueline MIKOL**

**Claire PAQUET**

**Marc POLIVKA**

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**Dominique HERVÉ**

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**Hugues CHABRIAT**

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**Katia DOSSOU**

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**Isabelle LEVESQUE**

**Claudine PORON**

**Suzanne PORTENGUEN**

**Aurélie SELVANADIN**

**Patrice CASTAGNET**

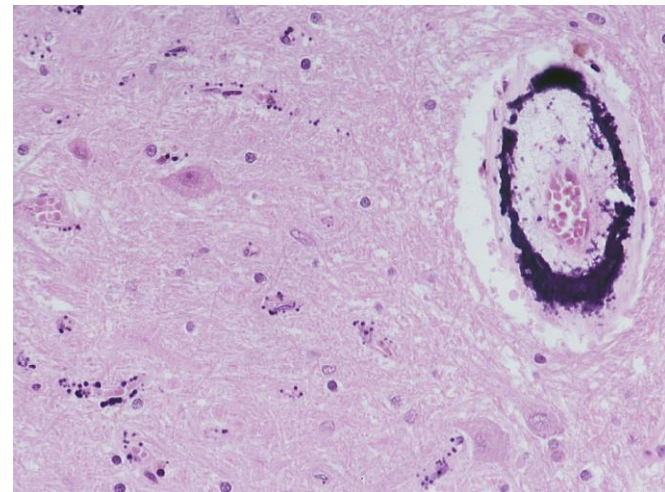
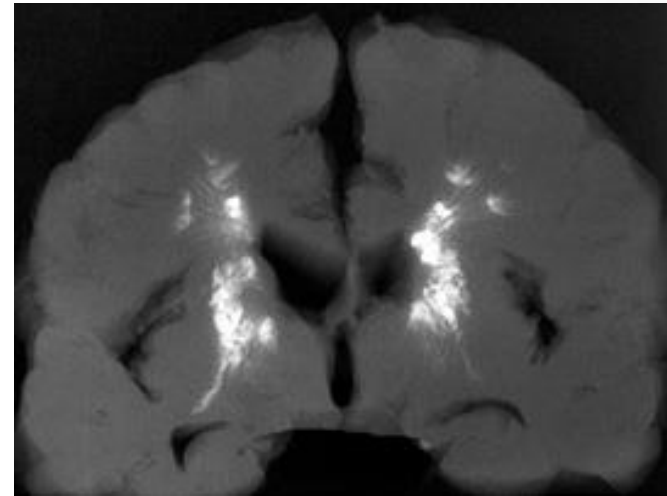
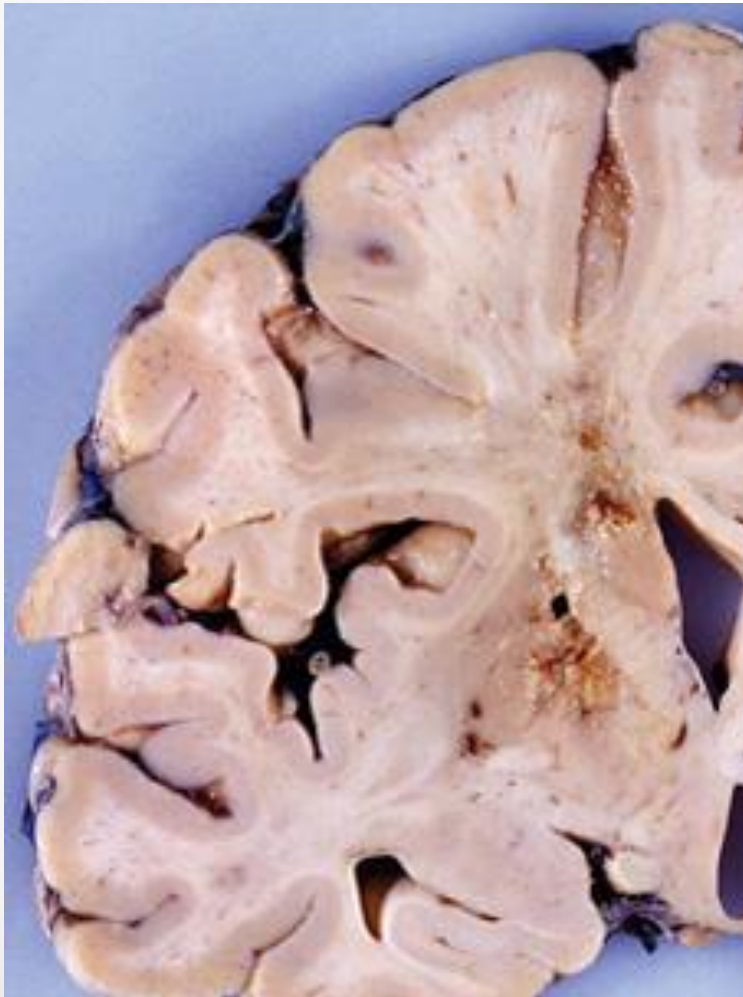




# Idiopathic basal ganglia calcification (IBGC)

- Calcifications in the basal ganglia are a common incidental finding at MRI or autopsy
- It is sometimes inherited as an autosomal dominant trait (idiopathic basal ganglia calcification IBGC or Fahr disease).
- Mutations in *SLC20A2* leading to **inactivation of the encoded inorganic phosphate transporter PIT2** have been linked to ~50% of IBGC cases

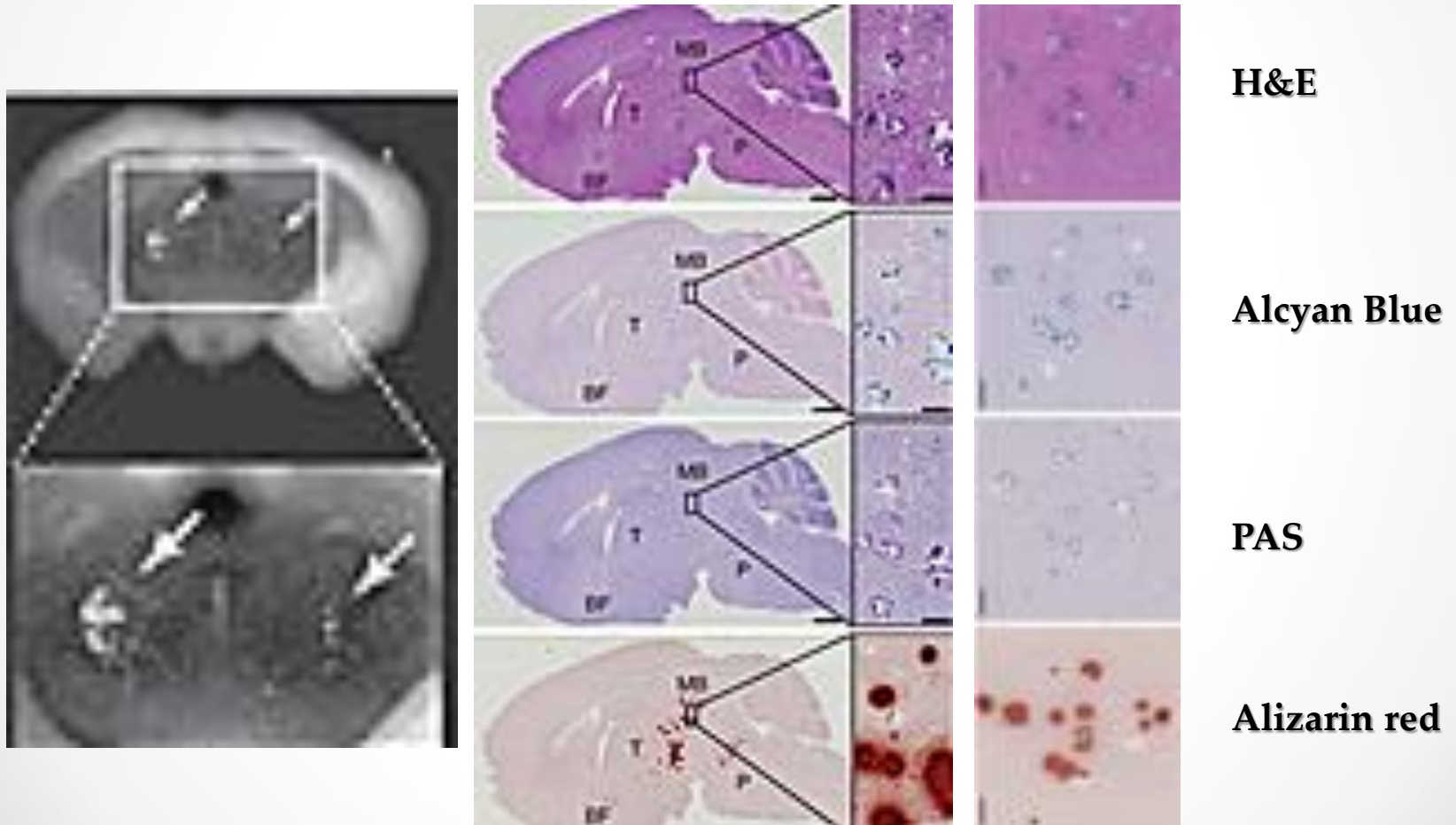
# Idiopathic basal ganglia calcification (IBGC)



# IBGC linked to *PDGFRB* and *PDGFB* mutations

- Recently, IBGC was linked to mutations in *PDGFRB*, the gene encoding the platelet-derived growth factor receptor  $\beta$  (PDGF-R $\beta$ ) and in *PDGFB*, the gene encoding PDGF-B, the main ligand for PDGF-R $\beta$
- PDGF-B is a growth factor for mesenchymal cells and has a particularly important role in the **recruitment of pericytes during angiogenesis**
- Interestingly, mice carrying hypomorphic *Pdgfb* alleles develop brain calcifications that show age-related expansion

# Brain calcifications in *Pdgfra*<sup>ret/ret</sup> mice



(Keller et al. Nature Genetics 2013; 45:1077-82)

**Small vessel diseases  
associated with  
Signal Transducer and  
Activator of Transcription 3  
(STAT3) Deficiency**

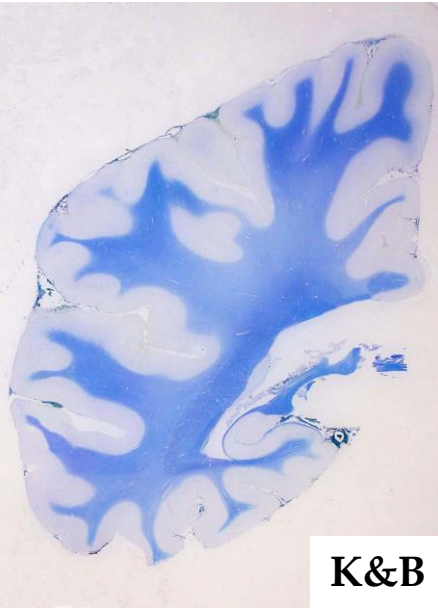
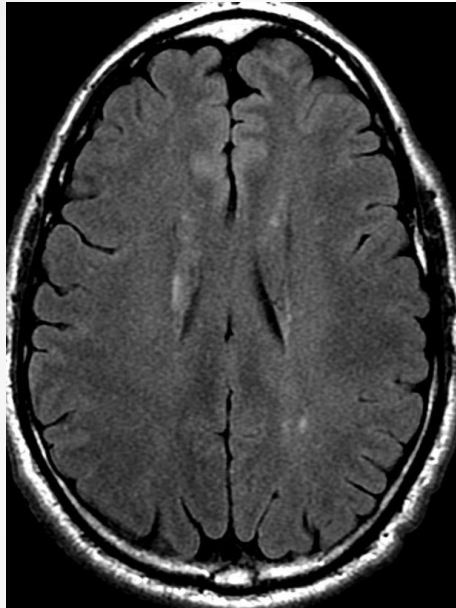
# STAT3 Deficiency

- Rare and complex **primary immunodeficiency** referred to as an autosomal dominant hyper-IgE syndrome caused by heterozygous mutations in the different domains of *STAT3*
- It is characterized by high immunoglobulin E (IgE) level, hypereosinophilia, memory B-cell lymphopenia, impaired IL-17 production by T cells and defective Th17 differentiation

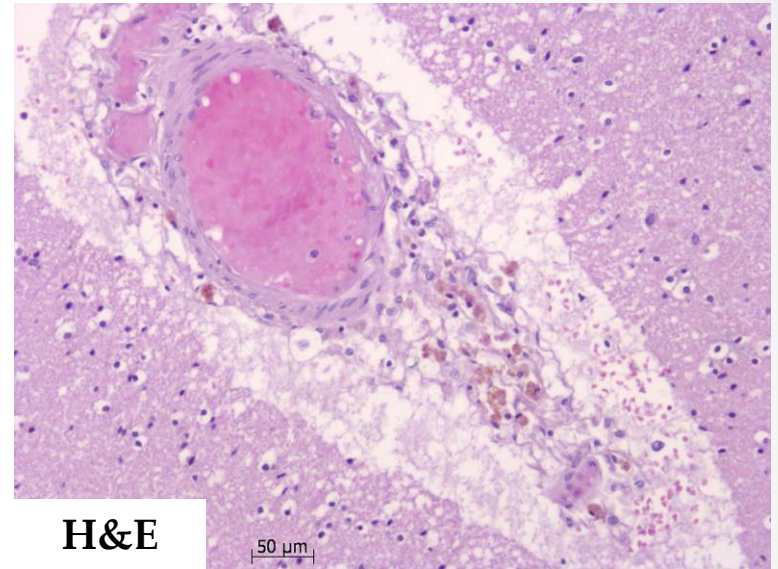
# STAT3 Deficiency

- **Connective tissue disease:** facial dysmorphism, impairment of the shedding of deciduous teeth, specific susceptibility to parenchymal lung damages, hyperextensibility, and bone abnormalities
- **Involvement of large vessels:** hypotrophic remodeling of the artery wall, with susceptibility to dilation and aneurysm formation particularly in heart and brain vessels
- **Involvement of small vessel of the brain with leukoencephalopathy**

# STAT3 Deficiency

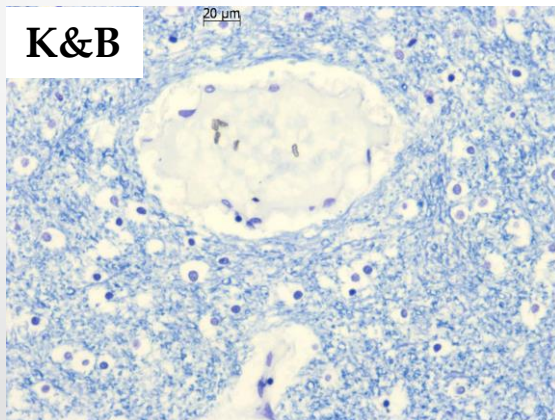


K&B



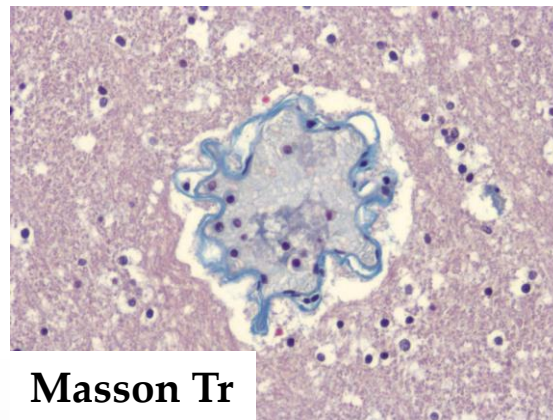
H&E

50 μm

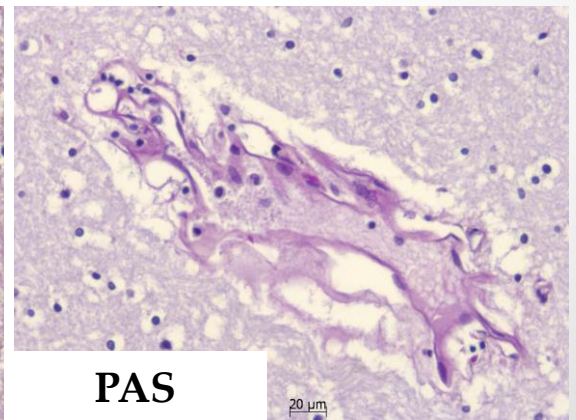


K&B

20 μm



Masson Tr



PAS

20 μm