CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

Genetics

-NOTCH3 (Neurogenic locus notch homolog protein 3; 19p13.2-p13.1)

-AD; mostly inherited; de novo is rare

Clinical findings/Dysmorphic features

-Stroks before age 60; cognitive disturbance; behavioral abnormalities; migraine with aura

Etiology

-Minimum prevalence 2-4 per 100,000

Pathogenesis

-NOTCH transmembrane receptors involved in cell fate specification during development

-Pathogenic variants --> loss or gain of a Cys in one of the 34 EGFr domains --> unpaired cys --> disrupted disulphide bridge formation --> aggregation of the mutant extracellular domain

Genetic testing/diagnosis

-Suspected: white matter hyperintensities + family history of stroke and/or vascular dementia

-Brain MRI: T2 signal abnormalities in the white matter of the temporal pole and external capsule, subcortical lacunar lesions

-Skin biopsy: electron microscopy shows characteristic granular osmophilic material (GOM) within the vascular media close to vascular smooth muscle cells (pathognomonic)

-Sequencing of NOTCH3 identifies pathogenic variants in >90%