Abstract  Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an inherited cerebrovascular disease due to mutations of the Notch3 gene at the chromosome locus 19p13. The clinical spectrum includes recurrent ischaemic episodes, cognitive deficits, migraine and psychiatric disorders. The histopathological hallmark of CADASIL is accumulation of electron dense granules (GOM) in the media of arterioles. MRI reveals extensive cerebral white matter lesions and subcortical infarcts. CADASIL was initially thought to be a rare disorder, but increasing numbers of families have been identified; therefore, it is likely that CADASIL is still largely underdiagnosed. Here we report an update on mutations of the Notch3 gene and some information on the pathogenesis of the disease.

Key words Stroke • Leucoencephalopathy • CADASIL • Molecular genetics • Mutations • NOTCH3

Introduction  Understanding of the pathogenesis of strokes in recent years has improved greatly, and many molecular genetic conditions related to this symptom have been found. Among them, there is strong interest in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL; OMIN 12310), firstly described by Tournier-Lasserve et al. [1], for its clinical heterogeneity, inheritance and frequency.

Clinical aspects  CADASIL is an autosomal dominant vascular disorder, clinically characterised by a variety of symptoms including migraine with aura, mood disorders, recurrent subcortical ischaemic strokes, progressive cognitive decline, dementia and premature death. The vascular lesions underlying CADASIL are a non-arteriosclerotic, non-amyloid arteriopathy affecting primarily small cerebral arteries, although the vascular defects are present in every tissue and may be detected histologically by examining arterioles in skin biopsy, where accumulation of granular and osmiophilic material within the smooth muscle cell basement membrane and the surrounding extracellular matrix have been reported.

MRI is characterised by hyperintense lesions on T2-weighted images in the subcortical white matter and basal ganglia. Skehan et al. studied MRI appearance in 10 individuals in one large Irish autosomal dominant family and found 2 major types of abnormalities. The most striking were large confluent patches of high-signal change on T2- and proton density-weighted images present throughout the white matter, especially in the anterior part of the temporal lobes and the periventricular portion of the occipital lobes. Additionally, they detected small linear and punctate lacunes present not only in the periventricular white matter.
but also in the brain stem, basal ganglia, thalamus, external capsule and corpus callosum [2] (Fig. 1).

More recently, Lesnik Oberstein et al., describing an increase in white matter hyperintensities on brain MRI compared to controls, confirmed that the characteristic pattern of lesions is located in the anterior temporal lobes, the frontal lobes and the periventricular caps [3].

The course of the disease is very heterogeneous, even in the same family: some patients remain asymptomatic until their 70s, whereas others are severely affected from the age of 50. A description of the clinical phenotype has been reported by Dichgans et al. [4].

**Molecular genetics**

CADASIL is caused by mutations in the NOTCH3 gene [5]. Notch3 is one of four mammalian homologues of *Drosophila* Notch. Notch genes code for large transmembrane receptors involved into cell fate decision during embryonic development. The Notch3 receptor is proteolytically processed in the trans-Golgi network as it traffics from the endoplasmic reticulum to the plasma membrane. Proteolytic cleavage results in a large extracellular fragment and a small intracellular fragment that contains the transmembrane region (Fig. 2a). Interaction of the Notch receptor with its ligand leads to cleavage of the transmembrane receptor which migrates into the nucleus and, associated with a transcription factor, activates transcription of primary target genes (Fig. 2b).

Like all Notch receptors, Notch3 contains a large number of tandemly arranged epidermal growth factor-like (EGF-like) repeat domains, which account for most of the extracellular part of protein. The gene consists of 34 exons, and all of them may have pathogenetic mutations (Fig. 3).

Numerous mutations in this gene have been described in recent years, giving a large genetic heterogeneity to the disease. Until now, no genotype–phenotype relationship has been described.