Cerebral Autosomal Dominant Arteriopathy with Subcortical Ischemic Strokes and Leukoencephalopathy (CADASIL)

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Abstract

Of these inherited small vessel diseases, cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL) is the most frequent single-gene disorder caused by the mutations in the Notch3 gene located on chromosome 19p13. This Notch3 gene has 33 exons, but almost CADASIL mutations are clustered in exons 2–24. More than 95% of these mutations are missense mutations and most of which involve gain or loss of cysteine residue. However, despite the debates, novel mutation of R75P, not involving a cysteine residue, was reported in Asian populations, thus broadening the spectrum of CADASIL. The main symptoms include subcortical ischemic events, migraine, progressive cognitive decline, seizure, and psychiatric features. Typical diagnostic criteria of neuroimaging show severe white-matter hyperintensities usually involving anterior part of the temporal lobe and external capsules.

In contrast, previous studies suggested differences in the clinical and genetic spectrum of CADASIL between Asians and Caucasian populations. While exon 4 was the major Notch3 mutation sites in Caucasian population, exon 11 was the most common in Asian population. Although it is unclear that genetic differences might affect the phenotypes in ethnicities, Asian population shows less migraine or seizure, but more intracerebral hemorrhage. Furthermore, especially in patients with R75P mutations, the sensitivity of MRI detecting anterior temporal pole abnormalities was lower.

The terminology of small vessel disease refers to the pathological process that occurs in the small vessels of brain, including small arteries, arterioles, small veins, and capillaries. However, the definition of small vessel disease is not uniform and is used to refer only to the arterial vessels of the brain [1]. There are different etiologies of small vessel diseases and one of the etiological classifications was proposed previously (Table 8.1) [1].

Of these inherited or genetic types, cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL) is the most frequent single-gene disorder of small cerebral arteries caused by the mutations in the Notch3 gene located on chromosome 19p13.

Although its overall prevalence is unknown, a small study from Scotland, UK, announced a prevalence of 4.15 cases per 100,000 [2].

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Table 8.1 Etiologic classification of small vessel diseases of brain [1]

Types	
Arteriolosclerosis	Fibrinoid necrosis, Lipohyalinosis, Microatheroma Microaneurysms, Segmental arterial disorganization
Sporadic and hereditary cerebral amyloid angiopathy	
Inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy	Cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy, cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy, hereditary multi-infarct dementia of the Swedish type, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary, endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by *COL4A1* mutations
Inflammatory and immunologically mediated small vessel diseases	Wegener's granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis, Henoch–Schonlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the central nervous system, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis
Venous collagenosis	
Other small vessel diseases	Post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer's disease

However, because many cases would not have been revealed, the actual prevalence of CADASIL could be much higher.

8.1 Molecular Genetic Analysis

Notch3 gene located in chromosome 19p13 encodes a single pass transmembrane receptor with an extracellular domain containing 34 tandem epidermal growth factor repeats (EGFR) (Fig. 8.1a). This Notch3 gene has 33 exons, but almost CADASIL mutations are clustered in exons 2–24. More than 95% of these mutations are missense mutations and over 150 mutations have been reported, most of which involve gain or loss of cysteine residue [3] (Fig. 8.1b).

However, novel mutation of R75P, not involving a cysteine residue, was reported in Asian populations, thus broadening the spectrum of CADASIL [4–6]. At present, there is still debate over whether the R75P mutation also causes CADASIL or not pathogenic polymorphism. Of note, although no evidence is available, previous report evaluating 27 Korean mutation carriers and family members suggest that this is a true mutation for following reasons: index patients had typical clinical and neuroimaging features

and some of them showed granular osmophilic granules (GOM) on skin biopsy. Furthermore, family members of patients with R75P mutation often had Notch3 mutations, typical symptoms, and MRI abnormalities, whereas the subjects without R75P mutation, none had typical CADASIL symptoms [4].

Although the clinical phenomenon of CADASIL varies, the clinical suspicion is based on the following main conditions: (1) onset at a young age (fifth to sixth decades); (2) absence of conventional stroke risk factors; (3) frequent lacunar infarctions with progressive white matter changes; (4) typical clinical symptoms such as migraine with aura, subcortical ischemic events, seizure, and cognitive impairment; (5) autosomal dominant inheritance [7]. The flowchart of CADASIL diagnosis is presented in Fig. 8.2.

8.2 Clinical Presentation

The range at onset of clinical symptoms is broad. The main symptoms include subcortical ischemic events, migraine, progressive cognitive decline, seizure, and psychiatric features. The temporal profile of main clinical presentations is presented in Fig. 8.3.
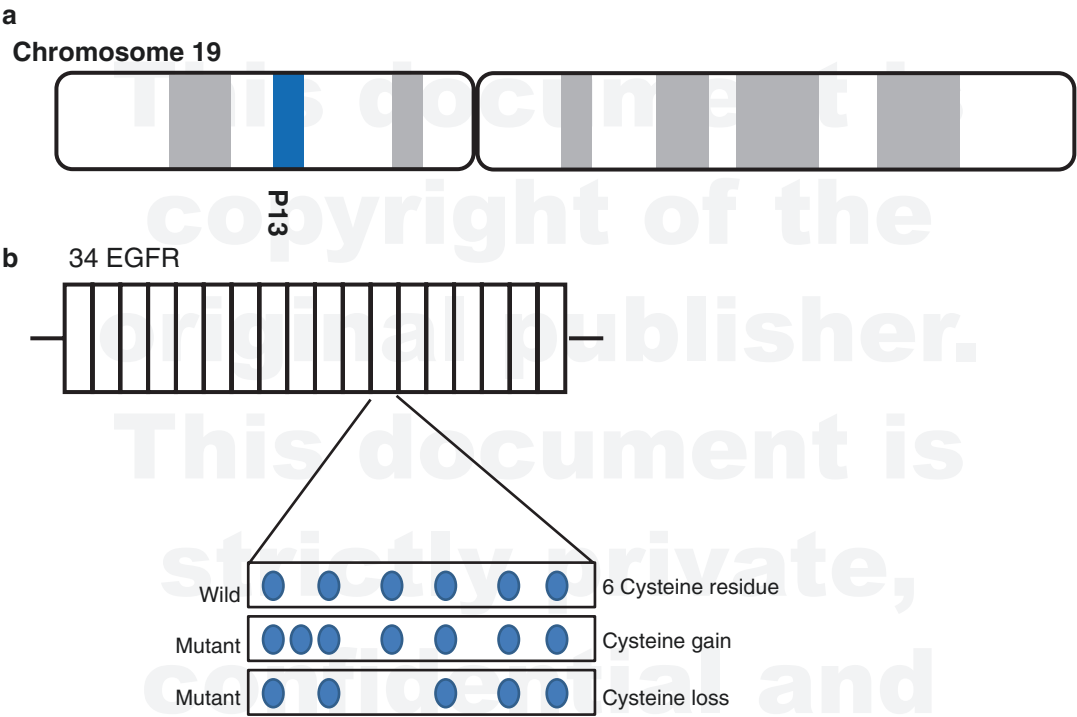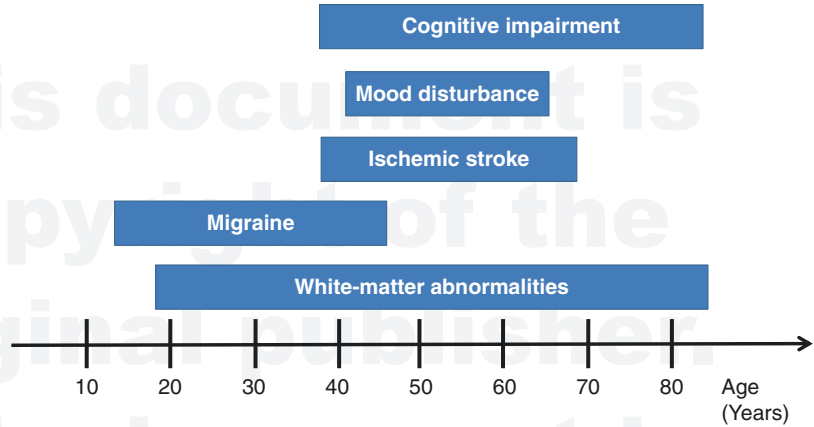
Fig. 8.1 Schematic drawing of Notch3 mutation. (**a**) genetic locus of Notch3 mutation on chromosome 19. (**b**) The epidermal growth factor like repeat (EGFR) and cysteine gain or loss [8]
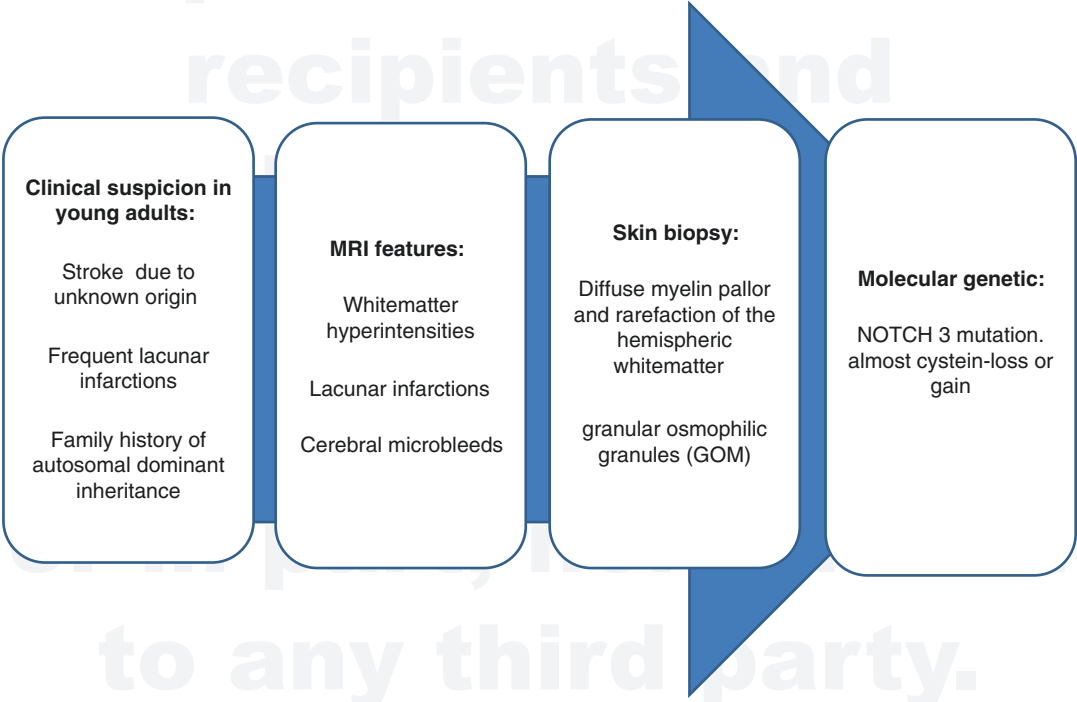
Fig. 8.2 Diagnostic keys for CADASIL

Fig. 8.3 Temporal profiles of the main clinical manifestations of CADASIL

8.2.1 Subcortical Ischemic Stroke

Ischemic strokes and transient ischemic attacks are the most frequent in CADASIL, occurring in approximately 85% of symptomatic subjects. These occur at mean age 45–50 years. Ischemic episodes are almost subcortical and typically present as a lacunar syndrome. In patients with severe subcortical ischemic strokes, diagnosis of CADASIL should be more considered, if there is no conventional risk factor. However, because some risk factors such as hypertension, dyslipidemia, and smoking are often accompanied, it is unclear whether this is associated with coincidental or CADASIL pathology [9, 10].

8.2.2 Intracerebral Hemorrhagic Stroke

CADASIL has been shown typically ischemic form, while intracerebral hemorrhage (ICH) has been rarely reported. Previous single center study in Korean population demonstrated that 25% of 20 consecutively enrolled patients with CADASIL had ICH [5]. It is unclear whether ICH in CADASIL patients developed as a process of diseases associated with specific gene. However, cerebral microbleeds (MBs) have been found in 31–69% of patients with CADASIL [11, 12]. Those might be found in various regions, but frequently found in

cortico-subcortical junction, thalamus, and brainstem [5, 11, 13]. Although the exact mechanisms of ICH in CADASIL patients are unknown currently, MBs and antithrombotics might be related to the increased risk of ICH [5, 14].

8.2.3 Migraine

Migraine is often the first feature, generally around 30 years (range from 6 to 48 years). It is reported in approximately 55–75% of Whites, while it is less frequent in Asians [4]. In a recent study in 378 CADASIL patients, a total of 54.5% of subjects had migraine and over four-fifth of these had migraine with aura [15]. By contrast, migraine without aura has the similar frequency in subjects with general population and CADASIL [3].

The exact patho-mechanism leading to increased migraine with aura is not clearly elucidated. One possible explanation is that Notch3 mutations increase susceptibility to spreading depression in cerebral cortex [16]. Another explanation is also possible that this is related to the brainstem region in CADASIL patients.

8.2.4 Cognitive Impairment

Cognitive impairment is the second major symptom of CADASIL. The earliest sign is reduced

processing speed and executive dysfunction, with relative preservation of episodic memory [17, 18]. Executive dysfunction is presented with a mean age of onset of 42 years. Memory impairment was reported later in the disease processing. Cognitive impairment more worsens with aging, and recurrent strokes [17, 18]. It is noteworthy that although cognitive decline is progressive, severe aphasia, agnosia, or apraxia is rarely reported [18].

8.2.5 Other Clinical Manifestations

Seizure has been described in 5–10% of CADASIL patients. It is usually presented with first symptom in a patient without known CADASIL and mainly related to the presence of an ischemic stroke [3, 11, 19].

Mood disturbances are reported in approximately 20% and are generally manifested as severe depressive mood. Because these episodes occur with manic episodes before typical MRI findings, physicians could mistake this for bipolar disease [19].

8.3 Neuroimaging

MRI findings in CADASIL patients shows age- and stage of disease-dependent features. Typical diagnostic criteria of neuroimaging show three types as follows: [1] severe white-matter hyperintensities usually involving anterior part of the temporal lobe and external capsules (Fig. 8.4a, b), [2] lacunar infarctions in centrum semiovale, thalamus, basal ganglia, and brainstem, [3] cerebral microbleeds [20]. Except for some cases, MRI changes may precede the initiation of other clinical symptoms by 10–15 years [3]. Many studies have demonstrated that typical anterior temporal and external capsule involvement could be diagnostic imaging markers for CADASIL [21]. According to a previous report, anterior temporal pole changes had high sensitivity and specificity (approximately 90% for each) and had a higher specificity than external capsular region (approximately 50%) [22, 23]. However, in Asian populations, anterior temporal hyperintensities have been shown less commonly involvement [4, 24].
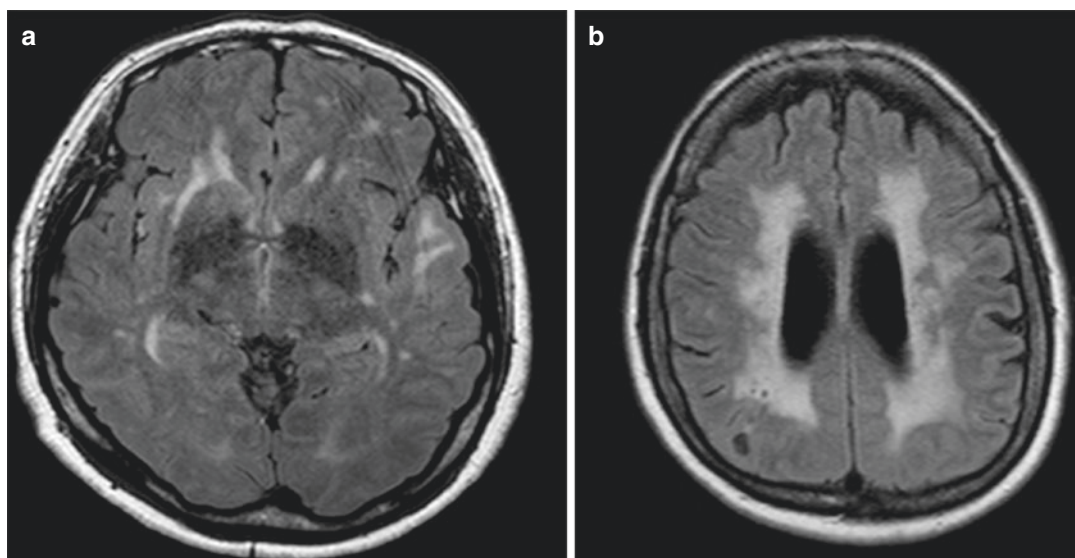
Fig. 8.4 Typical magnetic resonance imaging in CADASIL. (**a**) Hyperintensities in anterior temporal pole and external capsule. (**b**) Severe periventricular white-matter change and microbleeds

8.4   Characteristic Differences Between Caucasians and Asians

Previous studies suggested differences in the clinical and genetic spectrum of CADASIL between Asians and Caucasian populations. In Caucasian population with CADASIL, exon 4 was the major Notch3 mutation sites. Notch3 mutations were clustered in exons 2–6 [21]. While exon 3 is the second most common mutation site in British and French groups, exon 11 is the most frequently involved in Dutch population [21, 25, 26]. However, in Asian population, the most common Notch3 mutation was in exon 11, followed by exon 18, 4, and 3 [5, 24].

The "founder effect" is a special genetic drift, occurring when a small group was split off from the original population and established a new one, thus lost the genetic variation. These phenomenon have been reported in some inland or island areas, e.g., R544C in Koreans [5], R133C in Finland [27], and R607C in Italians [28] (Fig. 8.5).

8.5   Cystein Sparing CADASIL Mutations

Whether cystein sparing variants can cause CADASIL is still debated. However, R75P was described in many Asian families [4–6]. Despite a lot of controversies, based on earlier descried assumption [4], R75P could be considered the best explained cystein sparing Notch3 mutation to date.

Furthermore, recent study identified that another novel cystein sparing Notch3 mutation (D80G) in 4 German families [29]. These data can be considered to provide novel insights on the potential significance of cystein sparing Notch3 mutation.

Although it is unclear that genetic differences might affect the phenotypes in ethnicities, Asian population shows less frequent migraine or seizure. While approximately 40–50% of patients had migraine in Caucasians, only 5–10% of subjects in Asians had migraine [4, 21, 24]. ICH was relatively common in East Asians [24, 30].

Fig. 8.5   Several CADASIL founder mutations [8]

Table 8.2 Available treatment in CADASIL

Symptoms	Treatment
Migraine	Antiepileptic drugs (sodium valproate) Beta blockers Acetazolamide Conventional analgesics
Ischemic attacks	Antiplatelet drugs Treatment for vascular risk factors
Cognitive impairment	Acetylcholinesterase inhibitor

Especially in patients with R75P mutations, the sensitivity of MRI detecting anterior temporal pole abnormalities was lower than in sites where mutations occurred frequently in Caucasians [4, 24]. These results suggest that anterior temporal involvement cannot be a marker for diagnosis of CADASIL, at least in Asians.

8.6　Treatment

At present, there is no effective treatment for CADASIL. Therefore, the goal of treatment is to control clinical symptoms. In Table 8.2, available treatments for clinical presentations were summarized [3, 23].

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