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CADASIL

Synonym: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

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Summary

Clinical characteristics

CADASIL (*c*erebral *a*utosomal *d*ominant *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy) is characterized by mid-adult onset of recurrent ischemic stroke, cognitive decline progressing to dementia, a history of migraine with aura, mood disturbance, apathy, and diffuse white matter lesions and subcortical infarcts on neuroimaging.

Diagnosis/testing

The diagnosis of CADASIL is established in a proband either by identification of a heterozygous pathogenic variant in *NOTCH3* by molecular genetic testing or, if molecular genetic testing is not definitive, by detection of characteristic findings by electron microscopy and immunohistochemistry of a skin biopsy.

Management

Treatment of manifestations: There is no treatment of proven efficacy for CADASIL. Standard supportive treatment for stroke; the effect of thrombolytic therapy for the treatment of stroke remains unknown. Migraine should be treated symptomatically. Standard treatment for psychiatric disturbance. Supportive care (practical help, emotional support, and counseling) is appropriate for affected individuals and their families.

Prevention of primary manifestations: Antiplatelet therapy may be considered for prevention of stroke/TIA, but efficacy has not been proven. Anticoagulants should be avoided if possible. Control of vascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking). Prophylactic treatment of migraines, depending on the frequency.

Surveillance: Routine evaluation by a neurologist with expertise in CADASIL; consultation with a neuropsychiatrist if symptoms of depression, apathy, or psychiatric manifestations; consultation with other

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medical specialists (e.g., rehabilitation physician, clinical geneticist, physical therapist, and psychologist) as needed.

Agents to avoid: Thrombolytic therapy (intravenous thrombolysis) and oral anticoagulants probably increase the risk of intracerebral hemorrhage in individuals with CADASIL. These agents should therefore only be used carefully and on a case-by-case basis. Smoking increases the risk of stroke.

Pregnancy management: There may be an increased risk for neurologic events in pregnancy during and shortly after delivery (puerperium); transient neurologic events (migraine with aura) have most commonly been reported.

Genetic counseling

CADASIL is inherited in an autosomal dominant manner. Most affected individuals have an affected parent; *de novo* pathogenic variants appear to be rare. Each child of an affected person is at a 50% risk of inheriting the pathogenic variant and developing signs of the disease. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the pathogenic variant in the family is known.

Diagnosis

There are no generally accepted diagnostic criteria for CADASIL (*c*erebral *a*utosomal *d*ominant *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy). A CADASIL diagnostic screening tool has been proposed by Pescini et al [2012], Mizuta et al [2017], and Bersano et al [2018].

Suggestive Findings

CADASIL **should be suspected** in individuals with unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia; however, lack of an apparent family history of CADASIL does not preclude the diagnosis (see **Family history**). The following clinical signs and neuroimaging findings can be observed in CADASIL.

Clinical signs

- Transient ischemic attacks and ischemic stroke
- Cognitive impairment, manifesting initially with executive dysfunction, with a concurrent stepwise deterioration due to recurrent strokes to vascular dementia
- Migraine with aura, with a mean age of onset of 30 years
- Psychiatric disturbances, most frequently mood disturbances and apathy

Brain imaging

- Symmetric and progressive white matter hyperintensities, often involving the anterior temporal lobes and external capsules
- Lacunes of presumed vascular origin
- Recent subcortical infarcts
- Dilated perivascular spaces, sometimes referred to as subcortical lacunar lesions
- Brain atrophy
- Cerebral microbleeds

Family history consistent with autosomal dominant inheritance is suggestive. Note, however, that lack of an apparent family history of CADASIL does not preclude the diagnosis, as affected family members may have been misdiagnosed [Razvi et al 2005a] and *de novo* cases have been described [Joutel et al 2000, Coto et al 2006].

Establishing the Diagnosis

The diagnosis of CADASIL **is established** in a proband either by identification of a heterozygous pathogenic (or likely pathogenic) variant in *NOTCH3* by molecular genetic testing (see Table 1) or, if molecular genetic testing is not definitive, by detection of characteristic findings by electron microscopy and immunohistochemistry of a skin biopsy.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *NOTCH3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of CADASIL is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with recurrent stroke and/or dementia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of CADASIL, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *NOTCH3* (to include, at a minimum, exons 2-24) detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If a biallelic pathogenic variant is identified, consider gene-targeted deletion/duplication analysis to determine if an unidentified exon deletion or duplication is present.

  Note: Biallelic *NOTCH3* pathogenic variants have been described in individuals with CADASIL (see Genotype-Phenotype Correlations).

- **A multigene panel** that includes *NOTCH3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by stroke and/or dementia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are

likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in CADASIL

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
NOTCH3	Sequence analysis [3]	Estimated >95% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. When all exons coding for epidermal growth factor-like repeats (see Molecular Genetics) are sequenced (exons 2-24) and stringent inclusion criteria are applied [Markus et al 2002, Peters et al 2005a]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Rutten et al [2013]

Skin Biopsy

The diagnosis can be confirmed by ultrastructural analysis of small arterioles obtained, for example, by skin biopsy [Goebel et al 1997, Ruchoux & Maurage 1997]. Electron microscopy shows characteristic granular osmiophilic material (GOM) within the vascular media close to vascular smooth muscle cells. The detection of GOM is considered pathognomonic for CADASIL, but the reported sensitivity is variable [Tikka et al 2009, Morroni et al 2013].

NOTCH3 immunostaining of a skin biopsy shows a positive granular NOTCH3 staining of the vessel wall [Joutel et al 2001, Oberstein 2003].

The combined analysis by electron microscopy and immunohistochemistry, when interpreted by an experienced (neuro)pathologist, usually allows for a conclusive CADASIL diagnosis [Rutten et al 2014].

Clinical Characteristics

Clinical Description

CADASIL is a disease of the small to medium-sized arteries, mainly affecting the brain. The presenting symptoms, age at onset, and disease progression in CADASIL are variable, both between and within families. The disease is characterized by five main symptoms: transient ischemic attacks and recurrent ischemic strokes; cognitive decline; migraine with aura; mood disturbance; and apathy.

Subcortical ischemic events. Transient ischemic attacks (TIAs) and stroke, the most frequent presentation, are found in approximately 85% of symptomatic individuals [Dichgans et al 1998]. Mean age at onset for ischemic episodes is 47 years (age range 20-70 years) [Opherk et al 2004].

Ischemic episodes typically present as a classic lacunar syndrome (pure motor stroke, ataxic hemiparesis/dysarthria-clumsy hand syndrome, pure sensory stroke, sensorimotor stroke), but other lacunar syndromes

(brain stem or hemispheric) are also observed [Adib-Samii et al 2010]. Ischemic episodes are often recurrent, leading to severe disability with gait disturbance, urinary incontinence, and pseudobulbar palsy.

Strokes involving the territory of a large artery have occasionally been reported. However, whether these are coincidental observations, or whether (certain sub-populations of) individuals with CADASIL are at increased risk for large vessel stroke, is unclear [Choi et al 2013, Yin et al 2015, Kang & Kim 2015].

Cognitive deficits and dementia. Cognitive decline may start as early as age 35 years. Up to 75% of affected individuals develop dementia, often accompanied by apathy [Dichgans 2009, Reyes et al 2009].

The pattern of cognitive dysfunction is initially characterized by deficits in executive function (timed measures and measures of error monitoring), verbal fluency, and memory with benefit from clues [Peters et al 2005b]. Cognitive dysfunction is accompanied by a narrowing of the field of interest. In most cases, cognitive decline is slowly progressive, with some preservation of recognition and semantic memory, with additional stepwise deterioration. Visuospatial abilities and reasoning decline, especially after age 60. Cognitive decline becomes more apparent with aging and disease progression, ultimately leading to significant alterations in all cognitive domains at an older age [Buffon et al 2006]. Amberla et al [2004] observed deterioration of working memory and executive function in individuals with *NOTCH3* pathogenic variants in the pre-stroke phase and inferred that cognitive decline may start insidiously before the onset of symptomatic ischemic episodes.

Migraine, when present, can be the first symptom of CADASIL. Migraine occurs in 30%-75% of individuals with CADASIL, with the first attack occurring at a mean age of 26-29 years [Adib-Samii et al 2010, Tan & Markus 2016, Guey et al 2016]. Eighty to ninety percent of those with migraine have migraine with aura [Guey et al 2016, Tan & Markus 2016]. Migraine auras are sometimes confused with transient ischemic symptoms, since aura may include focal neurologic deficits [Di Donato et al 2017]. Sixty percent of those with migraine with aura have experienced an atypical migraine attack: prolonged, basilar or hemiplegic aura, confusion, fever, or coma [Guey et al 2016].

Psychiatric disorders. In most CADASIL cohorts, psychiatric disturbances are described in about one third of individuals [Adib-Samii et al 2010]. The reported prevalence of psychiatric disturbances is variable: a small study in 23 Italian patients recorded a lifetime risk for depression of 74% and a lifetime risk for a manic episode of 26% [Valenti et al 2011], whereas in a Chinese cohort, psychiatric manifestations were recorded in only 7% of affected individuals [Wang et al 2011]. Apathy has been described in 40% of individuals [Reyes et al 2009]. The psychiatric manifestations vary from personality changes to severe depression. The pathogenesis of psychiatric disturbances in CADASIL is incompletely understood. Psychiatric problems as a presenting symptom of CADASIL have been described [Leyhe et al 2005, Nakamura et al 2005, Park et al 2014].

Reversible acute encephalopathy. Acute encephalopathy has been described in some individuals, with confusion, headache, pyrexia, seizures, and coma, sometimes leading to death [Adib-Samii et al 2010, Ragno et al 2013, Tan & Markus 2016]. Migraine with aura (especially confusional aura) is associated with increased risk of acute encephalopathy, suggesting that they may share pathophysiologic mechanisms [Tan & Markus 2016].

Epilepsy. Epilepsy occurs in 10% of individuals with CADASIL and presents in middle age, usually secondary to stroke [Haan et al 2007]. In a pooled analysis of previous published cases, three of 105 individuals with CADASIL had a seizure as the initial presenting symptom [Desmond et al 1999].

Pregnancy. It has been suggested that the risk for migraine with aura is increased during pregnancy, but especially during puerperium (the period between childbirth and the return of the uterus to its normal size) [Roine et al 2005]. Another study found no association between pregnancy and risk for neurologic events or problems during pregnancy [Donnini et al 2017]. See Pregnancy Management.

Other findings

- **Cardiac.** Controversy exists as to whether CADASIL is associated with cardiac involvement. In a study from The Netherlands, nearly 25% of individuals with CADASIL had a history of acute myocardial infarction (MI) and/or current pathologic Q-waves on electrocardiogram (EKG) [Lesnik Oberstein et al 2003]. This percentage was significantly higher than in controls without a heterozygous *NOTCH3* pathogenic variant. However, another study of 23 individuals with CADASIL found no signs of previous MI on EKG [Cumurciuc et al 2006b]. Two studies have suggested an increased risk for arrhythmias, based on increased QT variability on EKG recording [Rufa et al 2007, Piccirillo et al 2008].
- **Nerve.** Nerve biopsies may demonstrate signs of axonal damage, demyelination, and ultrastructural changes of the endoneurial blood vessels [Schröder et al 2005, Sicurelli et al 2005, Lackovic et al 2012]. Punch skin biopsies from individuals with CADASIL showed cutaneous somatic and autonomic nerve involvement [Nolano et al 2016]. Clinically, however, there is no clear evidence that peripheral neuropathy is part of the CADASIL clinical spectrum [Kang et al 2009].
- **Ocular.** Subclinical retinal lesions are reported [Cumurciuc et al 2004, Haritoglou et al 2004]. Fundoscopy may reveal clinically silent retinal vascular abnormalities [Pretegiani et al 2013]. Optical coherence tomography imaging techniques may show reduced subfoveal choroidal thickness, retinal arterial luminal narrowing, retinal venous luminal enlargement, and reduced vessel density of the deep retinal plexus [Alten et al 2014, Fang et al 2017, Nelis et al 2018].
- **Renal.** NOTCH3 accumulation and granular osmiophilic material (GOM) are also detected in renal arteries, and stenosis of renal arteries has been described [Ragno et al 2012, Lorenzi et al 2017]. Although no large-scale studies have been published regarding kidney function in individuals with CADASIL, to date there is no evidence that kidney function is affected [Bergmann et al 1996].

Long-term prognosis and causes of death. Onset of symptoms and overall survival may vary based on the type of pathogenic variant and its location within *NOTCH3* (see Genotype-Phenotype Correlations).

Data on the long-term prognosis in CADASIL come from a large study of 411 individuals [Opherk et al 2004], which found that the median age at onset of inability to walk without assistance was approximately 60 years and the median age at which individuals became bedridden was 64 years. The median age at death was 68 years with a more rapid disease progression in men than in women. Pneumonia was the most frequent cause of death, followed by sudden unexpected death and asphyxia. In the final stages of disease, 78% of individuals were completely dependent and 63% were confined to bed.

The median survival time of men was significantly shorter than expected from German life tables, whereas the median survival time of women was not significantly reduced. The reason for this difference is not known; possible explanations include sex hormones, sex differences in risk factor control, medical management, social support, and socioeconomic factors.

Brain imaging. Imaging abnormalities in CADASIL evolve as the disease progresses [van den Boom et al 2003, Singhal et al 2005, Liem et al 2008a]:

- In individuals age 20-30 years, distinctive white matter hyperintensities often first appear in the anterior temporal lobes, when the rest of the white matter, except for periventricular caps, appears unaffected [Oberstein 2003, van den Boom et al 2003].
- In the course of the disease, the load of white matter hyperintensity lesions increases, eventually coalescing to the point where, in some elderly individuals, normal-appearing white matter is barely distinguishable [Chabriat et al 1998].
- White matter hyperintensities in the temporal lobe and external capsule are characteristic for CADASIL but not always present [O'Sullivan et al 2001, Markus et al 2002]. Involvement of the anterior temporal lobe is highly suggestive for CADASIL; this finding, however, is not sensitive or specific for the diagnosis of CADASIL [Sureka &Jakkani 2012].

- In symptomatic individuals, white matter hyperintensities are symmetrically distributed and located in the periventricular and deep white matter. Within the white matter, the frontal lobe is the site with the highest lesion load, followed by the temporal and parietal lobes [Auer et al 2001, O'Sullivan et al 2001].
- The majority of lacunes develop at the edge of white matter hyperintensities and proximal to white matter hyperintensities along the course of perforating vessels supplying the respective brain region [Duering et al 2013].
- Brain atrophy appears to result from accumulation of lacunes and widespread microstructural alterations within the brain [Jouvent et al 2007].
- Lacunes and brain atrophy are strongly correlated with clinical severity and clinical worsening in individuals with CADASIL [Ling et al 2018, Jouvent et al 2016].
- Dilated perivascular spaces are found in approximately 70%-80% of affected individuals [van Den Boom et al 2002, Cumurciuc et al 2006a, Yao et al 2014].
- Cerebral microbleeds (CMB) are reported in approximately one third of affected individuals [Puy et al 2017, Nannucci et al 2018]. Cerebral microbleeds do not have a clear predominant location in individuals with CADASIL. In a study of 125 affected individuals, cerebral microbleeds were present in 34%. Of these, 29% had CMB in the deep subcortical region (most frequently in the thalamus), 22% in the lobar region (especially the temporal lobe), and 18% in the infratentorial region [Nannucci et al 2018].

Other imaging studies. Positron emission tomography, transcranial Doppler sonography, and perfusion MRI may show decreased cerebral blood flow, decreased cerebral blood volume, impaired cerebral metabolism, decreased vasoreactivity, and altered neurovascular coupling [Tatsch et al 2003, Tuominen et al 2004, Huneau et al 2018, Moreton et al 2018].

Pathophysiology. Cerebral blood supply in individuals with CADASIL is reduced below demand, as demonstrated by an increased oxygen extraction rate in asymptomatic and demented individuals with CADASIL. Cerebral blood flow, cerebral blood volume, and cerebral glucose utilization are significantly reduced [Bruening et al 2001, Tuominen et al 2004]. In addition, cerebral vasoreactivity is impaired [Pfefferkorn et al 2001], consistent with the observed degeneration of vascular smooth muscle cells in small arteries and arterioles [Kalimo et al 2002]. Increased fragility of cerebral microvessels is suggested by a high frequency of cerebral microbleeds at autopsy and on gradient echo MRI [Lesnik Oberstein et al 2001, Dichgans et al 2002].

Genotype-Phenotype Correlations

Smaller studies have described genotype-phenotype correlations for specific pathogenic variants [Lesnik Oberstein et al 2001, Arboleda-Velasquez et al 2002, Opherk et al 2004, Bianchi et al 2010]; however, none of these associations have been firmly established.

In general, affected individuals with cysteine-altering pathogenic variants in epidermal growth-factor like repeat (EGFr) domains 1-6 of NOTCH3 have a 12-year earlier onset of stroke, lower survival, and increased white matter hyperintensity volume, consistent with the more severe classic CADASIL presentation, compared to those with a cysteine-altering pathogenic variant in EGFr domains 7-34. The mean survival time was 68.5 and 76.9 years, respectively [Rutten et al 2019].

There is conflicting evidence about the effect of pathogenic variants in the ligand-binding domain of *NOTCH3* (EGFr domains 10 and 11). Both a more severe and a milder phenotype have been described in small series [Arboleda-Velasquez et al 2002, Monet-Leprêtre et al 2009, Rutten et al 2019] (see also Penetrance).

Biallelic pathogenic variants in *NOTCH3* have been described in individuals with CADASIL [Tuominen et al 2001, Liem et al 2008b, Ragno et al 2013, Soong et al 2013, Vinciguerra et al 2014, Abou Al-Shaar et al 2016]. The phenotype of individuals with biallelic *NOTCH3* pathogenic variants falls within the CADASIL spectrum.

Penetrance

Pathogenic variants in EGFr domains 1-6 appear to be fully penetrant and are usually associated with the classic CADASIL phenotype. However, there is variability in disease severity.

Pathogenic variants in EGFr domains 7-34 have a much higher population frequency (~1:300) [Rutten et al 2016a, Rutten et al 2019] and therefore likely predispose to a milder small-vessel disease and may even be non-penetrant.

Nomenclature

Previous descriptions of families with "hereditary multi-infarct dementia," "chronic familial vascular encephalopathy," and "familial subcortical dementia" represent early reports of CADASIL.

Prevalence

While most published information on individuals with CADASIL originates from Europe, CADASIL has been observed on all continents. Multiple small and national European registries have estimated the minimum prevalence at between two and four per 100,000 [Kalimo et al 2002, Razvi et al 2005b, Narayan et al 2012, Bianchi et al 2015].

Recently, it was found that the frequency of *NOTCH3* cysteine-altering pathogenic variants is 1:300 in the general population worldwide (gnomAD), with the highest frequency in people who are from Asian descent (1:100) [Rutten et al 2016a, Rutten et al 2019]. This is approximately 100-fold higher than current estimates of the minimum prevalence of CADASIL, suggesting that CADASIL is much more prevalent than previously suspected and that the *NOTCH3* clinical spectrum must be considerably broader, ranging from classic CADASIL to a much milder small-vessel disease, or possibly even non-penetrance.

Genetically Related (Allelic) Disorders

Heterozygous truncating pathogenic variants in *NOTCH3* exon 33 (encoding the PEST domains of the intracellular part of the protein) have been described in Lateral Meningocele Syndrome (Lehman syndrome). These pathogenic variants are presumed to act via a gain of NOTCH3 signaling function and are distinct from *NOTCH3* pathogenic variants in CADASIL [Gripp et al 2015].

A *NOTCH3* heterozygous exon 25 variant has been described in autosomal dominant infantile myofibromatosis (OMIM 615293) [Martignetti et al 2013].

Differential Diagnosis

The differential diagnosis of CADASIL includes sporadic/multifactorial disorders and inherited disorders.

Sporadic/Multifactorial Disorders

The clinical characteristics and MRI abnormalities in these conditions may resemble those of CADASIL. The presence of temporopolar MRI lesions, the absence of optic nerve and spinal cord involvement, the absence of oligoclonal bands in the cerebrospinal fluid, and the absence of hypertension are critical in this regard [Dichgans et al 1999] (see Table 2).

Table 2. Clinical Signs and MRI Abnormalities of Sporadic/Multifactorial Disorders in the Differential Diagnosis of CADASIL

Disorder	Distinguishing Clinical Characteristics	Distinguishing MRI Abnormalities	Temporopolar MRI Lesions	Optic Nerve & Spinal Cord Involvement	Oligoclonal Bands in CSF	Hypertension
Multiple sclerosis [1]	• Optic neuritis • Spinal cord involvement • Internuclear ophthalmoplegia • Lhermitte sign • Heat sensitivity • Age of onset: 15-50 yrs	• Juxtacortical WMH • Dawson fingers • Spinal cord, corpus callosum & U-fibers involvement • Gadolinium enhancement of lesions	Common	Typical	Yes	Not associated
Sporadic small vessel disease incl Binswanger's disease	• Hypertension • Absence of AD or AR inheritance in family history • Age of onset: >65 yrs	• Involvement of temporal pole is rare • Involvement of external capsule occurs less frequently	Rare	No	No	Associated
Primary angiitis of the nervous system [2]	• Subacute headache • Multifocal neurologic deficits • Signs & symptoms suggestive of systemic vaculitis (peripheral neuropathy, fever, weight loss, rash, & night sweats) • May occur at any age; median age at diagnosis: 50 yrs	• Multifocal infarcts in different vascular territories • Diffuse gadolinium enhanced lesions	Uncommon	Involvement of: • Spinal cord: 5% of affected individuals • Optic nerve: rare	Occasionally	Not associated

AD = autosomal dominant; AR = autosomal recessive; CSF = cerebrospinal fluid; WMH = white matter hyperintensities

1. Joshi et al [2017]

2. Williamson et al [1999]

Inherited Disorders

Several inherited disorders are associated with acute ischemic events (or stroke-like episodes in the case of MELAS) and cerebral white matter hyperintensities on MRI. These disorders can be distinguished from CADASIL by the associated clinical signs, MRI, mode of inheritance, and appropriate laboratory investigations (particularly, molecular genetic testing) (see Table 3).

Table 3. Clinical Signs and MRI Abnormalities of Inherited Disorders to Consider in the Differential Diagnosis of CADASIL

Disorder	Gene(s)	MOI	Distinguishing Clinical Signs	Distinguishing MRI Abnormalities
Fabry disease	*GLA*	XL	Classic Fabry disease phenotype: • Onset in childhood & adolescence • Periodic severe pain in extremities • Angiokeratoma • Renal insufficiency • Hypohidrosis • Cardiac involvement • Corneal opacities Late-onset Fabry disease phenotype: • Onset in adulthood & later • Cardiomyopathy • Renal disease • Cerebrovascular disease	• Exclusive involvement of pulvinar thought to be characteristic • Ischemic strokes predominantly located in vertebrobasilar system • Vertebrobasilar dolichoectasia
CARASIL [1]	*HTRA1*	AR	• Onset age: 20-30 yrs (spastic gait) • Spastic gait • Premature alopecia • Severe low back pain & deforming spondylosis	• Spinal spondylosis • In advanced stage: "arc" sign (involvement of pontocerebellar tract)
HTRA1 cerebral small vessel disease (CADASIL type 2)		AD	• Onset age: 50-70 yrs (stroke) • Alopecia, spondylosis, & low back pain reported (less frequently than in CARASIL)	Spinal spondylosis
MELAS [2]	*MT-TL1* *MT-ND5* [3]	Mat	• Onset age: 2-10 yrs • Anorexia • Recurrent vomiting • Short stature • Generalized tonic-clonic seizures • Proximal limb weakness • Sensorineural hearing loss • Stroke-like episodes of cortical blindness and/or altered consciousness from age ~40 yrs	• ↑ T_2 signal, involving the posterior cerebrum, not conforming to the distribution of major arteries • Swollen gyri • Gadolinium enhancement of lesions • Slow spreading of stroke-like lesions
CARASAL [4]	*CTSA*	AD	• Age of onset: 40-60 yrs • Intracerebral hemorrhage • Muscle cramps • Xerostomia • Keratoconjuctivitis sicca • Therapy-resistant hypertension	Intracerebral hemorrhages

Table 3. continued from previous page.

Disorder	Gene(s)	MOI	Distinguishing Clinical Signs	Distinguishing MRI Abnormalities
COL4A1- & *COL4A2*-related small vessel disease (see *COL4A1*-Related Disorders & OMIM PS175780) [5]	*COL4A1* *COL4A2*	AD	Highly variable clinical spectrum; onset range: infantile to (late) adult. Infantile onset: • Psychomotor retardation • Infantile hemiplegia • Intracerebral hemorrhage • Seizures Adult onset: • Intracerebral hemorrhage • Opthalmologic abnormalities • Renal abnormalities • Cardiovascular abnormalties • Muscle cramps	• Porencephaly • Schizencephaly • Deep & lobar intracerebral hemorrhage • Cerebral calcification • Cerebellar atrophy • Intracranial aneurysms

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance; WMH = white matter hyperintensities; XL = X-linked
1. CARASIL = *c*erebral *a*utosomal *r*ecessive *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy
2. MELAS = *m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes
3. Pathogenic variants known to cause MELAS have been identified in other mtDNA tRNA genes including *MT-TC*, *MT-TK*, *MT-TV*, *MT-TF*, *MT-TQ*, *MT-TS1*, *MT-TS2*, and *MT-TW*, and in the protein-encoding genes *MT-CO1*, *MT-CO2*, *MT-CO3*, *MT-CYB*, *MT-ND1*, *MT-ND3*, and *MT-ND6*.
4. CARASAL = cathepsin A–related arteriopathy with strokes and leukoencephalopathy [Bugiani et al 2016]
5. Meuwissen et al [2015]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CADASIL, the following evaluations are recommended, if they have not already been completed.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with CADASIL

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic eval	
	Standard brain MRI incl FLAIR sequence & T_2-weighted gradient echo imaging	To determine extent of disease & establish baseline measure for follow up
Neurodevelopmental	Psychometrics	W/particular attention to executive function
Psychiatric/ Behavioral	Consider referral to a psychiatrist.	For treatment of mood disorders & eval of apathy
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	• Assess use of community or online resources. • Social work involvement for support • Home nursing referral, if needed

Treatment of Manifestations

Discussion of medical management options for individuals with CADASIL have been published [del Río-Espínola et al 2009, Di Donato et al 2017].

Table 5. Treatment of Manifestations in Individuals with CADASIL

Manifestation/ Situation	Treatment	Considerations/Other
Acute stroke/ TIA	Standard supportive treatment following stroke medicine guidelines	Effect of thrombolytic therapy (IV thrombolysis) unknown; no evidence or rationale for thrombolysis in those w/CADASIL, & risk of intracerebral hemorrhage is probably ↑; see Agents/ Circumstances to Avoid.
Migraine	Symptomatic treatment; may incl triptans & ergot derivatives	NO evidence that triptans or ergot derivatives are contraindicated due to their vasoconstrictive mechanism of action [1]
Psychiatric disturbance	Standard treatment [2]	Psychometric & psychiatric eval can be used to evaluate whether apathy (if present) is a symptom of depression or of cognitive dysfunction.

IV = intravenous; TIA = transient ischemic attack

1. Triptans appear to have the same treatment responses and frequency of serious side effects in individuals with CADASIL as in the general migraine population [Tan & Markus 2016].

2. No studies have been performed in individuals with CADASIL to determine the effect of the treatment of psychiatric disturbances (e.g. depression) with psychiatric drugs.

Prevention of Primary Manifestations

No treatment is of proven efficacy in preventing stroke, vascular dementia, or CADASIL disease progression.

Table 6. Prevention of Primary Manifestations in Individuals with CADASIL

Manifestation/ Situation	Prevention	Considerations/Other
Stroke/TIA	Consider antiplatelet therapy. [1]	Effect of antiplatelet therapy in persons w/CADASIL unknown; no evidence or rationale for its use in treatment of CADASIL – though also no evidence that it is contraindicated.
	Control of vascular risk factors	Incl hypertension, diabetes, hypercholesterolemia, & smoking
Migraine	Consider prophylactic therapy.	Depending on migraine frequency

1. Such as aspirin and clopidogrel

Surveillance

No standard international surveillance guidelines for CADASIL exist. Several countries have developed CADASIL guidelines, such as the medical guideline for CADASIL published (in French) by the French Health Authority (HAS).

The interval at which individuals with CADASIL should be seen for follow up depends on the severity and type of symptoms and the needs of patients and their care givers.

- Follow up by a neurologist with expertise in CADASIL is recommended from the time of diagnosis onward.
- A consultation with a neuropsychiatrist is recommended when there are symptoms of depression, apathy, or other psychiatric manifestations.

- Consultation of other medical specialists (e.g., rehabilitation physician, clinical geneticist, physical therapist, and psychologist) is as required.

Agents/Circumstances to Avoid

The treatment effect of thrombolytic therapy (intravenous thrombolysis) is unknown in individuals with CADASIL. Studies performed in non-CADASIL populations show that increasing cerebral microbleed burden and increasing white matter hyperintensity lesion load is associated with an increased risk of intracerebral hemorrhage after thrombolytic therapy [Charidimou et al 2016, Charidimou et al 2017b]; therefore, individuals with CADASIL may be at increased risk for intracerebral hemorrhage. In case of a thromboembolic large vessel stroke (i.e., unrelated to CADASIL), the benefit of thrombolysis outweighs the potential risk of intracerebral hemorrhage.

Oral anticoagulants could lead to an increased risk of intracerebral hemorrhage in individuals with CADASIL due to the presence of microbleeds [Charidimou et al 2017a]; the prescription of anticoagulants should therefore be carefully weighed. In case of a clear indication for anticoagulant therapy, such as atrial fibrillation or deep venous thrombosis, the benefit of the treatment likely outweighs the potential risk of intracerebral hemorrhage.

Smoking increases the risk of stroke in individuals with CADASIL and should be avoided [Singhal et al 2004].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Fetuses affected with CADASIL are not at an increased risk for intrauterine complications or complications during/after delivery [Donnini et al 2017].

In a retrospective study, women with CADASIL were at increased risk for neurologic events in pregnancy during and shortly after delivery (puerperium) [Roine et al 2005]. However, another retrospective study of 50 affected women and prospectively collected data of six women showed no association between CADASIL and risk for neurologic events or problems during pregnancy [Donnini et al 2017]. In the authors' experience, most women with CADASIL have an uncomplicated pregnancy and delivery, but transient neurologic events are sometimes reported (mostly consistent with migraine aura) [Lesnik Oberstein, unpublished observation based on clinical practice].

Therapies Under Investigation

Case reports and small-scale observational studies have suggested a beneficial effect of acetazolamide on migraine [Weller et al 1998, Forteza et al 2001, Donnini et al 2012]. Acetazolamide has also been shown to have a beneficial effect on cerebral perfusion [Chabriat et al 2000, Huang et al 2010, Park et al 2011, Fujiwara et al 2012]. Acetazolamide is not given to individuals with CADASIL on a routine basis, as no large studies have been performed.

Several therapeutic approaches are in pre-clinical development: testing in cells and mouse models including immunotherapy [Machuca-Parra et al 2017, Ghezali et al 2018], antisense mediated *NOTCH3* exon skipping [Rutten et al 2016b], and treatment with stem cell factor and granulocyte colony-stimulating factor [Liu et al 2015].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

Cross-sectional and longitudinal studies suggest that disease progression is faster in individuals with CADASIL who have increased blood pressure [Peters et al 2004, Holtmannspötter et al 2005, Peters et al 2006, Ling et al 2017]. However, no controlled data regarding the effect of antihypertensive treatment on disease progression are available.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

CADASIL is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with CADASIL have an affected parent, although a negative family history is occasionally reported.
- A proband with CADASIL may have the disorder as the result of a new pathogenic variant. Two individuals with *de novo* pathogenic variants have been reported [Joutel et al 2000, Coto et al 2006]; the authors have seen four individuals with *de novo* pathogenic variants in clinical practice [Authors, personal observations].
- The recommended evaluation of apparently asymptomatic parents of an individual with CADASIL who has a known *NOTCH3* pathogenic variant is molecular genetic testing. (Note that genetic testing of asymptomatic parents should be performed in the context of formal genetic counseling as such testing constitutes predictive testing.)
- An apparently negative family history cannot be confirmed until appropriate evaluations have been performed:
  - A family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.
  - A review of family histories by Razvi et al [2005a] found that a false negative family history was common for individuals presenting with features of CADASIL. They conclude that restriction of family history to premature stroke alone is probably inadequate to identify affected CADASIL pedigrees.
- Biallelic pathogenic variants in *NOTCH3* have been described in individuals with CADASIL [Tuominen et al 2001, Liem et al 2008b, Ragno et al 2013, Soong et al 2013, Vinciguerra et al 2014, Abou Al-Shaar et al 2016, Mukai et al 2018]. In such cases, both parents of a proband may have a *NOTCH3* pathogenic variant.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If one of the parents is affected, as is true for the vast majority of individuals with a *NOTCH3* pathogenic variant, the risk to sibs is 50%.

- If the proband has biallelic *NOTCH3* pathogenic variants and both parents are heterozygous, the risk to the sibs of the proband of having at least one *NOTCH3* pathogenic variant and being affected is 75%.
- If the *NOTCH3* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.
- If both parents are clinically unaffected but have not been tested for the *NOTCH3* pathogenic variant, the sibs of a proband are still at increased risk for CADASIL because of the possibility of late onset of CADASIL in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with a *NOTCH3* pathogenic variant has a 50% chance of inheriting the pathogenic variant.
- Each child of an individual who has biallelic *NOTCH3* pathogenic variants will inherit one of the pathogenic variants.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *NOTCH3* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of CADASIL, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *NOTCH3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CADASIL are possible.

Differences in perspectives may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **CADASIL Support UK**
  110 Heathmoor Park Road
  Halifax West Yorkshire HX2 9LP
  United Kingdom
  Email: info@cadasilsupport.co.uk
  www.cadasilsupportuk.co.uk

- **CADASIL Together We Have Hope Nonprofit Organization**
  3605 Monument Drive
  Round Rock TX 78681
  Phone: 800-617-8387
  Email: info@cadasilfoundation.org
  www.cadasilfoundation.org

- **Cambridge Stroke**
  CADASIL website

- **cureCADASIL Association**
  10 Schalks Crossing Road
  Suite 501A-133
  Plainsboro NJ 08536
  www.curecadasil.org

- **L'association CADASIL France**
  France
  www.cadasil.fr

- **MedlinePlus**
  CADASIL

- **Stichting Platform CADASIL**
  www.cadasil.eu
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  www.ulf.org
- **CADASIL Family Registry**
  Email: registry@cadasilassociation.org
  www.curecadasilfamilyregistry.com
- **CADASIL Together We Have Hope Registry**
  3605 Monument Drive
  Round Rock TX 78681
  Phone: 877-519-4673; 512-255-0209
  Email: info@cadasilfoundation.org
  www.cadasilfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. CADASIL: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NOTCH3	19p13.12	Neurogenic locus notch homolog protein 3	Notch homolog 3 (NOTCH3) @ LOVD	NOTCH3	NOTCH3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for CADASIL (View All in OMIM)

125310	CEREBRAL ARTERIOPATHY, AUTOSOMAL DOMINANT, WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY, TYPE 1; CADASIL1
600276	NOTCH RECEPTOR 3; NOTCH3

Gene structure. *NOTCH3* (NM_000435.2) consists of 33 exons spanning about 7 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in CADASIL are detected in exons 2-24. The majority of sequence alterations in *NOTCH3* are missense variants (95%), characteristically leading to the loss or gain of a cysteine residue in one of the 34 epidermal growth factor-like repeat (EGFr) domains of neurogenic locus notch homolog protein 3 (NOTCH3), the protein encoded by *NOTCH3* [Dichgans et al 2001]. This results in an uneven number of cysteine residues in the given EGFr domain, most likely modifying the tertiary structure of the protein.

Approximately 70% of European individuals with a clinical CADASIL diagnosis have a pathogenic variant in one of the exons encoding EGFr domains 1-6 [Rutten et al 2019], although regional differences are seen [Federico et al 2005, Bianchi et al 2015, Yin et al 2015, Chen et al 2017, Rutten et al 2019]. Pathogenic variants in EGFr domains 7-34 are less frequently seen in diagnosed individuals (~30%) but have a high frequency in the general

population (gnomAD) [Rutten et al 2019] – suggesting that only a small proportion of individuals with a pathogenic variant in EGFr 7-34 develop a classic CADASIL phenotype.

Of note, with a few exceptions [Mizuno et al 2008, Wollenweber et al 2015], there is no convincing evidence that missense variants not involving a cysteine residue cause CADASIL [Rutten et al 2014].

A few splice site variants, insertions, and deletions, predicted to result in an uneven number of cysteine residues within EGFr, have been associated with disease [Rutten et al 2014].

Table 7. Notable *NOTCH3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000435.2 NP_000426.2	c.397C>T	p.Arg133Cys	Finnish founder variant [Mykkänen et al 2004]
	c.1630C>T	p.Arg544Cys	Chinese founder variant [Lee et al 2009]
	c.3016C>T	p.Arg1006Cys	Marche region of Italy founder variant [Bianchi et al 2015]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The NOTCH signaling pathway is an evolutionarily conserved intercellular signaling mechanism that plays a central role during vascular development and physiology. NOTCH3 is primarily expressed in vascular smooth muscle cells and plays an important role in vascular smooth muscle cell differentiation and maturation [Domenga et al 2004], and in the control of vascular mechano-transduction [Belin de Chantemèle et al 2008]. NOTCH3 is a single pass transmembrane protein which consists of 2321 amino acids (NP_000426.2). The extracellular domain is composed of 34 EGFr domains and three Lin/Notch (LNR) repeats. It can bind to a ligand via the ligand binding domain, which consists of EGFr domain 10 and 11. The NOTCH3 protein also has an intracellular domain required for signal transduction.

Abnormal gene product. *NOTCH3* pathogenic variants in CADASIL lead to loss or gain of a cysteine residue in one of the protein's 34 EGFr domains. This results in an unpaired cysteine residue and disrupted disulphide bridge formation, causing aggregation of the mutant NOTCH3 extracellular domain. This, directly or indirectly, has a toxic effect, leading to degeneration of VSMC. It has been proposed that VSMC degeneration is due increased VSMC death [Gray et al 2007]. However, studies also showed that CADASIL VSMCs have a lower proliferation rate than control VSMCs [Viitanen et al 2013], due to increased transforming growth factor-β (TGFβ) expression [Panahi et al 2018]. Recent evidence indicates that the NOTCH3 aggregates cause sequestration of functionally important extracellular matrix proteins, such as vitronectin and tissue inhibitor of metalloproteinase-3 (TIMP3) [Monet-Leprêtre et al 2013].

Whether and which hypomorphic *NOTCH3* variants may cause a CADASIL-like phenotype is still unclear as these variants have been described in individuals both with and without small vessel disease. [Rutten et al 2013, Moccia et al 2015].

Overall, evidence from studies in human, mice, and cell models indicates that neomorphic properties of mutant NOTCH3 protein drive CADASIL pathogenesis, whereas loss of NOTCH3 function does not play a pivotal role [Rutten et al 2013, Cognat et al 2014].

Cancer and benign tumors. *NOTCH3* amplification and rearrangement has been observed in cancerous tissues obtained from normal individuals suggesting NOTCH3 plays a role in tumorigenesis [Boelens et al 2014, Jung et al 2014].

Chapter Notes

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References

Published Guidelines / Consensus Statements

- Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 3-30-23.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset disorders. Available online. 2018. Accessed 3-30-23.

Literature Cited

Abou Al-Shaar H, Qadi N, Al-Hamed MH, Meyer BF, Bohlega S. Phenotypic comparison of individuals with homozygous or heterozygous mutation of NOTCH3 in a large CADASIL family. J Neurol Sci. 2016;367:239–43. PubMed PMID: 27423596.

Adib-Samii P, Brice G, Martin RJ, Markus HS. Clinical spectrum of CADASIL and the effect of cardiovascular risk factors on phenotype: study in 200 consecutively recruited individuals. Stroke. 2010;41:630–4. PubMed PMID: 20167921.

Alten F, Motte J, Ewering C, Osada N, Clemens CR, Kadas EM, Eter N, Paul F, Marziniak M. Multimodal retinal vessel analysis in CADASIL patients. PLoS One. 2014;9:e112311. PubMed PMID: 25372785.

Amberla K, Waljas M, Tuominen S, Almkvist O, Poyhonen M, Tuisku S, Kalimo H, Viitanen M. Insidious cognitive decline in CADASIL. Stroke. 2004;35:1598–602. PubMed PMID: 15143298.

Arboleda-Velasquez JF, Lopera F, Lopez E, Frosch MP, Sepulveda-Falla D, Gutierrez JE, Vargas S, Medina M, Martinez De Arrieta C, Lebo RV, Slaugenhaupt SA, Betensky RA, Villegas A, Arcos-Burgos M, Rivera D, Restrepo JC, Kosik KS. C455R notch3 mutation in a Colombian CADASIL kindred with early onset of stroke. Neurology. 2002;59:277–9. PubMed PMID: 12136071.

Auer DP, Putz B, Gossl C, Elbel G, Gasser T, Dichgans M. Differential lesion patterns in CADASIL and sporadic subcortical arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. Radiology. 2001;218:443–51. PubMed PMID: 11161160.

Belin de Chantemèle EJ, Retailleau K, Pinaud F, Vessières E, Bocquet A, Guihot AL, Lemaire B, Domenga V, Baufreton C, Loufrani L, Joutel A, Henrion D. Notch3 is a major regulator of vascular tone in cerebral and tail resistance arteries. Arterioscler Thromb Vasc Biol. 2008;28:2216–24. PubMed PMID: 18818417.

Bergmann M, Ebke M, Yuan Y, Brück W, Mugler M, Schwendemann G. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): a morphological study of a German family. Acta Neuropathol. 1996;92:341–50. PubMed PMID: 8891065.

Bersano A, Bedini G, Markus HS, Vitali P, Colli-Tibaldi E, Taroni F, Gellera C, Baratta S, Mosca L, Carrera P, Ferrari M, Cereda C, Grieco G, Lanfranconi S, Mazucchelli F, Zarcone D, De Lodovici ML, Bono G, Boncoraglio GB, Parati EA, Calloni MV, Perrone P, Bordo BM, Motto C, Agostoni E, Pezzini A, Padovani A, Micieli G, Cavallini A, Molini G, Sasanelli F, Sessa M, Comi G, Checcarelli N, Carmerlingo M, Corato M, Marcheselli S, Fusi L, Grampa G, Uccellini D, Beretta S, Ferrarese C, Incorvaia B, Tadeo CS, Adobbati L, Silani V, Faragò G, Trobia N, Grond-Ginsbach C, Candelise L. Lombardia GENS-group. The role of clinical and neuroimaging features in the diagnosis of CADASIL. J Neurol. 2018;265:2934–43. PubMed PMID: 30311053.

Bianchi S, Rufa A, Ragno M, D'Eramo C, Pescini F, Pantoni L, Cappelli A, Perretti A, Zicari E, Zolo P, Inzitari D, Dotti MT, Federico A. High frequency of exon 10 mutations in the NOTCH3 gene in Italian CADASIL families: phenotypic peculiarities. J Neurol. 2010;257:1039–42. PubMed PMID: 20169447.

Bianchi S, Zicari E, Carluccio A, Di Donato I, Pescini F, Nannucci S, Valenti R, Ragno M, Inzitari D, Pantoni L, Federico A, Dotti MT. CADASIL in central Italy: a retrospective clinical and genetic study in 229 patients. J Neurol. 2015;262:134–41. PubMed PMID: 25344745.

Boelens MC, Wu TJ, Nabet BY, Xu B, Qiu Y, Yoon T, Azzam DJ, Twyman-Saint VC, Wiemann BZ, Ishwaran H, Ter Brugge PJ, Jonkers J, Slingerland J, Minn AJ. Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. Cell. 2014;159:499–513. PubMed PMID: 25417103.

Bruening R, Dichgans M, Berchtenbreiter C, Yousry T, Seelos KC, Wu RH, Mayer M, Brix G, Reiser M. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: decrease in regional cerebral blood volume in hyperintense subcortical lesions inversely correlates with disability and cognitive performance. AJNR Am J Neuroradiol. 2001;22:1268–74. PubMed PMID: 11498413.

Buffon F, Porcher R, Hernandez K, Kurtz A, Pointeau S, Vahedi K, Bousser MG, Chabriat H. Cognitive profile in CADASIL. J Neurol Neurosurg Psychiatry. 2006;77:175–80. PubMed PMID: 16421118.

Bugiani M, Kevelam SH, Bakels HS, Waisfisz Q, Ceuterick-de Groote C, Niessen HW, Abbink TE, Lesnik Oberstein SA, van der Knaap MS. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL). Neurology. 2016;87:1777–86. PubMed PMID: 27664989.

Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, Tournier-Lasserve E, Bousser MG. Patterns of MRI lesions in CADASIL. Neurology. 1998;51:452–7. PubMed PMID: 9710018.

Chabriat H, Pappata S, Ostergaard L, Clark CA, Pachot-Clouard M, Vahedi K, Jobert A, Le Bihan D, Bousser MG. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. Stroke. 2000;31:1904–12. PubMed PMID: 10926955.

Charidimou A, Karayiannis C, Song TJ, Orken DN, Thijs V, Lemmens R, Kim J, Goh SM, Phan TG, Soufan C, Chandra RV, Slater LA, Haji S, Mok V, Horstmann S, Leung KT, Kawamura Y, Sato N, Hasebe N, Saito T,

Wong LKS, Soo Y, Veltkamp R, Flemming KD, Imaizumi T, Srikanth V, Heo JH; International META-MICROBLEEDS Initiative. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology. 2017a;89:2317–26. PubMed PMID: 29117953.

Charidimou A, Pasi M, Fiorelli M, Shams S, von Kummer R, Pantoni L, Rost N. Leukoaraiosis, cerebral hemorrhage, and outcome after intravenous thrombolysis for acute ischemic stroke: a meta-analysis (v1). Stroke. 2016;47:2364–72. PubMed PMID: 27491738.

Charidimou A, Turc G, Oppenheim C. Yan S1, Scheitz JF, Erdur H, Klinger-Gratz PP, El-Koussy M, Takahashi W, Moriya Y, Wilson D, Kidwell CS, Saver JL, Sallem A, Moulin S, Edjlali-Goujon M, Thijs V, Fox Z, Shoamanesh A, Albers GW, Mattle HP, Benavente OR, Jäger HR, Ambler G, Aoki J, Baron JC, Kimura K, Kakuda W, Takizawa S, Jung S, Nolte CH, Lou M, Cordonnier C, Werring DJ. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis: individual patient data meta-analysis. Stroke. 2017b;48:2084–90. PubMed PMID: 28720659.

Chen S, Ni W, Yin XZ, Liu HQ, Lu C, Zheng QJ, Zhao GX, Xu YF, Wu L, Zhang L, Wang N, Li HF, Wu ZY. Clinical features and mutation spectrum in Chinese patients with CADASIL: A multicenter retrospective study. CNS Neurosci Ther. 2017;23:707–16. PubMed PMID: 28710804.

Choi JC, Song SK, Lee JS, Kang SY, Kang JH. Diversity of stroke presentation in CADASIL: study from patients harboring the predominant NOTCH3 mutation R544C. J Stroke Cerebrovasc Dis. 2013;22:126–31. PubMed PMID: 21852154.

Cognat E, Baron-Menguy C, Domenga-Denier V, Cleophax S, Fouillade C, Monet-Leprêtre M, Dewerchin M, Joutel A. Archetypal Arg169Cys mutation in NOTCH3 does not drive the pathogenesis in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy via a loss-of-function mechanism. Stroke. 2014;45:842–9. PubMed PMID: 24425116.

Coto E, Menendez M, Navarro R, Garcia-Castro M, Alvarez V. A new de novo Notch3 mutation causing CADASIL. Eur J Neurol. 2006;13:628–31. PubMed PMID: 16796587.

Cumurciuc R, Guichard JP, Reizine D, Gray F, Bousser MG, Chabriat H. Dilation of Virchow-Robin spaces in CADASIL. Eur J Neurol. 2006a;13:187–90. PubMed PMID: 16490051.

Cumurciuc R, Henry P, Gobron C, Vicaut E, Bousser MG, Chabriat H, Vahedi K. Electrocardiogram in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy patients without any clinical evidence of coronary artery disease: a case-control study. Stroke. 2006b;37:1100–2. PubMed PMID: 16514092.

Cumurciuc R, Massin P, Paques M, Krisovic V, Gaudric A, Bousser MG, Chabriat H. Retinal abnormalities in CADASIL: a retrospective study of 18 patients. J Neurol Neurosurg Psychiatry. 2004;75:1058–60. PubMed PMID: 15201374.

del Río-Espínola A, Mendióroz M, Domingues-Montanari S, Pozo-Rosich P, Solé E, Fernández-Morales J, Fernández-Cadenas I, Montaner J. CADASIL management or what to do when there is little one can do. Expert Rev Neurother. 2009;9:197–210. PubMed PMID: 19210195.

Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL: a pooled analysis of previously published cases. Stroke. 1999;30:1230–3. PubMed PMID: 10356105.

Dichgans M. Cognition in CADASIL. Stroke. 2009;40:S45–7. PubMed PMID: 19064778.

Dichgans M, Filippi M, Bruning R, Iannucci G, Berchtenbreiter C, Minicucci L, Uttner I, Crispin A, Ludwig H, Gasser T, Yousry TA. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. Neurology. 1999;52:1361–7. PubMed PMID: 10227618.

Dichgans M, Herzog J, Gasser T. NOTCH3 mutation involving three cysteine residues in a family with typical CADASIL. Neurology. 2001;57:1714–7. PubMed PMID: 11706120.

Dichgans M, Holtmannspotter M, Herzog J, Peters N, Bergmann M, Yousry TA. Cerebral microbleeds in CADASIL: a gradient-echo magnetic resonance imaging and autopsy study. Stroke. 2002;33:67–71. PubMed PMID: 11779891.

Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, Ebke M, Klockgether T, Gasser T. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol. 1998;44:731–9. PubMed PMID: 9818928.

Di Donato I, Bianchi S, De Stefano N, Dichgans M, Dotti MT, Duering M, Jouvent E, Korczyn AD, Lesnik-Oberstein SA, Malandrini A, Markus HS, Pantoni L, Penco S, Rufa A, Sinanović O, Stojanov D, Federico A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as a model of small vessel disease: update on clinical, diagnostic, and management aspects. BMC Med. 2017;15:41. PubMed PMID: 28231783.

Domenga V, Fardoux P, Lacombe P, Monet M, Maciazek J, Krebs LT, Klonjkowski B, Berrou E, Mericskay M, Li Z, Tournier-Lasserve E, Gridley T, Joutel A. Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. Genes Dev. 2004;18:2730–5. PubMed PMID: 15545631.

Donnini I, Nannucci S, Valenti R, Pescini F, Bianchi S, Inzitari D, Pantoni L. Acetazolamide for the prophylaxis of migraine in CADASIL: a preliminary experience. J Headache Pain. 2012;13:299–302. PubMed PMID: 22367627.

Donnini I, Rinnoci V, Nannucci S, Valenti R, Pescini F, Mariani G, Bianchi S, Dotti MT, Federico A, Inzitari D, Pantoni L. Pregnancy in CADASIL. Acta Neurol Scand. 2017;136:668–71. PubMed PMID: 28608406.

Duering M, Csanadi E, Gesierich B, Jouvent E, Hervé D, Seiler S, Belaroussi B, Ropele S, Schmidt R, Chabriat H, Dichgans M. Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease. Brain. 2013;136:2717–26. PubMed PMID: 23864274.

Fang XJ, Yu M, Wu Y, Zhang ZH, Wang WW, Wang ZX, Yuan Y. Study of Enhanced Depth Imaging Optical Coherence Tomography in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. Chin Med J (Engl). 2017;130:1042–8. PubMed PMID: 28469098.

Federico A, Bianchi S, Dotti MT. The spectrum of mutations for CADASIL diagnosis. Neurol Sci. 2005;26:117–24. PubMed PMID: 15995828.

Forteza AM, Brozman B, Rabinstein AA, Romano JG, Bradley WG. Acetazolamide for the treatment of migraine with aura in CADASIL. Neurology. 2001;57:2144–5. PubMed PMID: 11739850.

Fujiwara Y, Mizuno T, Okuyama C, Nagakane Y, Watanabe-Hosomi A, Kondo M, Kuriyama N, Tokuda T, Matsushima S, Nishimura T, Nakagawa M. Simultaneous impairment of intracranial and peripheral artery vasoreactivity in CADASILpatients. Cerebrovasc Dis. 2012;33:128–34. PubMed PMID: 22179564.

Ghezali L, Capone C, Baron-Menguy C, Ratelade J, Christensen S. Østergaard Pedersen L, Domenga-Denier V, Pedersen JT, Joutel A. Notch3^{ECD} immunotherapy improves cerebrovascular responses in CADASIL mice. Ann Neurol. 2018;84:246–59. PubMed PMID: 30014602.

Goebel HH, Meyermann R, Rosin R, Schlote W. Characteristic morphologic manifestation of CADASIL, cerebral autosomal- dominant arteriopathy with subcortical infarcts and leukoencephalopathy, in skeletal muscle and skin. Muscle Nerve. 1997;20:625–7. PubMed PMID: 9140375.

Gray F, Polivka M, Viswanathan A, Baudrimont M, Bousser MG, Chabriat H. Apoptosis in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neuropathol Exp Neurol. 2007;66:597–607. PubMed PMID: 17620985.

Gripp KW, Robbins KM, Sobreira NL, Witmer PD, Bird LM, Avela K, Makitie O, Alves D, Hogue JS, Zackai EH, Doheny KF, Stabley DL, Sol-Church K. Truncating mutations in the last exon of NOTCH3 cause lateral meningocele syndrome. Am J Med Genet A. 2015;167A:271–81. PubMed PMID: 25394726.

Guey S, Mawet J, Hervé D, Duering M, Godin O, Jouvent E, Opherk C, Alili N, Dichgans M, Chabriat H. Prevalence and characteristics of migraine in CADASIL. Cephalalgia. 2016;36:1038–47. PubMed PMID: 26646784.

Haan J, Lesnik Oberstein SA, Ferrari MD. Epilepsy in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Cerebrovasc Dis. 2007;24:316–7. PubMed PMID: 17675836.

Haritoglou C, Hoops JP, Stefani FH, Mehraein P, Kampik A, Dichgans M. Histopathological abnormalities in ocular blood vessels of CADASIL patients. Am J Ophthalmol. 2004;138:302–5. PubMed PMID: 15289148.

Holtmannspötter M, Peters N, Opherk C, Martin D, Herzog J, Bruckmann H, Samann P, Gschwendtner A, Dichgans M. Diffusion magnetic resonance histograms as a surrogate marker and predictor of disease progression in CADASIL: a two-year follow-up study. Stroke. 2005;36:2559–65. PubMed PMID: 16269644.

Huang L, Yang Q, Zhang L, Chen X, Huang Q, Wang H. Acetazolamide improves cerebral hemodynamics in CADASIL. J Neurol Sci. 2010;292:77–80. PubMed PMID: 20227091.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Huneau C, Houot M, Joutel A, Béranger B, Giroux C, Benali H, Chabriat H. Altered dynamics of neurovascular coupling in CADASIL. Ann Clin Transl Neurol. 2018;5:788–802. PubMed PMID: 30009197.

Joshi S, Yau W, Kermode A. CADASIL mimicking multiple sclerosis: The importance of clinical and MRI red flags. J Clin Neurosci. 2017;35:75–7. PubMed PMID: 27773545.

Joutel A, Dodick DD, Parisi JE, Cecillon M, Tournier-Lasserve E, Bousser MG. De novo mutation in the Notch3 gene causing CADASIL. Ann Neurol. 2000;47:388–91. PubMed PMID: 10716263.

Joutel A, Favrole P, Labauge P, Chabriat H, Lescoat C, Andreux F, Domenga V, Cecillon M, Vahedi K, Ducros A, Cave-Riant F, Bousser MG, Tournier-Lasserve E. Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. Lancet. 2001;358:2049–51. PubMed PMID: 11755616.

Jouvent E, Duchesnay E, Hadj-Selem F, De Guio F, Mangin JF, Hervé D, Duering M, Ropele S, Schmidt R, Dichgans M, Chabriat H. Prediction of 3-year clinical course in CADASIL. Prediction of 3-year clinical course in CADASIL. Neurology. 2016;87:1787–95. PubMed PMID: 27694265.

Jouvent E, Viswanathan A, Mangin JF, O'Sullivan M, Guichard JP, Gschwendtner A, Cumurciuc R, Buffon F, Peters N, Pachaï C, Bousser MG, Dichgans M, Chabriat H. Brain atrophy is related to lacunar lesions and tissue microstructural changes in CADASIL. Brain atrophy is related to lacunar lesions and tissue microstructural changes in CADASIL. Stroke. 2007;38:1786–90. PubMed PMID: 17446424.

Jung JG, Stoeck A, Guan B, Wu RC, Zhu H, Blackshaw S, Shih I, Wang TL. Notch3 Interactome Analysis Identified WWP2 as a Negative Regulator of Notch3 Signaling in Ovarian Cancer. PLoS Genet. 2014;10:e1004751. PubMed PMID: 25356737.

Kalimo H, Ruchoux MM, Viitanen M, Kalaria RN. CADASIL: a common form of hereditary arteriopathy causing brain infarcts and dementia. Brain Pathol. 2002;12:371–84. PubMed PMID: 12146805.

Kang HG, Kim JS. Intracranial arterial disease in CADASIL patients. J Neurol Sci. 2015;359:347–50. PubMed PMID: 26671140.

Kang SY, Oh JH, Kang JH, Choi JC, Lee JS. Nerve conduction studies in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neurol. 2009;256:1724–7. PubMed PMID: 19488673.

Lackovic V, Bajcetic M, Lackovic M, Novakovic I, Labudović Borović M, Pavlovic A, Zidverc-Trajkovic J, Dzolic E, Rovcanin B, Sternic N, Kostic V. Skin and sural nerve biopsies: ultrastructural findings in the first genetically confirmed cases of CADASIL in Serbia. Ultrastruct Pathol. 2012;36:325–35. PubMed PMID: 23025651.

Lee YC, Liu CS, Chang MH, Lin KP, Fuh JL, Lu YC, Liu YF, Soong BW. Population-specific spectrum of NOTCH3 mutations, MRI features and founder effect of CADASIL in Chinese. J Neurol. 2009;256:249–55. PubMed PMID: 19242647.

Lesnik Oberstein SA, Jukema JW, Van Duinen SG, Macfarlane PW, van Houwelingen HC, Breuning MH, Ferrari MD, Haan J. Myocardial infarction in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Medicine (Baltimore). 2003;82:251–6. PubMed PMID: 12861102.

Lesnik Oberstein SA, van den Boom R, van Buchem MA, van Houwelingen HC, Bakker E, Vollebregt E, Ferrari MD, Breuning MH, Haan J. Cerebral microbleeds in CADASIL. Neurology. 2001;57:1066–70. PubMed PMID: 11571335.

Leyhe T, Wiendl H, Buchkremer G, Wormstall H. CADASIL: underdiagnosed in psychiatric patients? Acta Psychiatr Scand. 2005;111:392–6. PubMed PMID: 15819734.

Liem MK, Lesnik Oberstein SA, Haan J, van der Neut IL, van den Boom R, Ferrari MD, van Buchem MA, van der Grond J. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: progression of MR abnormalities in prospective 7-year follow-up study. Radiology. 2008a;249:964–71. PubMed PMID: 18840792.

Liem MK, Lesnik Oberstein SA, Vollebregt MJ, Middelkoop HA, van der Grond J, Helderman-van den Enden AT. Homozygosity for a NOTCH3 mutation in a 65-year-old CADASIL patient with mild symptoms: a family report. J Neurol. 2008b;255:1978–80. PubMed PMID: 19153638.

Ling Y, De Guio F, Duering M, Jouvent E, Hervé D, Godin O, Dichgans M, Chabriat H. Predictors and Clinical Impact of Incident Lacunes in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy. Stroke. 2017;48:283–9. PubMed PMID: 28034964.

Ling Y, De Guio F, Jouvent E, Duering M, Hervé D, Guichard JP, Godin O, Dichgans M, Chabriat H. Clinical correlates of longitudinal MRI changes in CADASIL. J Cereb Blood Flow Metab. 2018 Feb 5:271678X18757875

Liu XY, Gonzalez-Toledo ME, Fagan A, Duan WM, Liu Y, Zhang S, Li B, Piao CS, Nelson L, Zhao LR. Stem cell factor and granulocyte colony-stimulating factor exhibit therapeutic effects in a mousemodel of CADASIL. Neurobiol Dis. 2015;73:189–203. PubMed PMID: 25251607.

Lorenzi T, Ragno M, Paolinelli F, Castellucci C, Scarpelli M, Morroni M. CADASIL: Ultrastructural insights into the morphology of granular osmiophilic material. Brain Behav. 2017;7:e00624. PubMed PMID: 28293466.

Machuca-Parra AI, Bigger-Allen AA, Sanchez AV, Boutabla A, Cardona-Vélez J, Amarnani D, Saint-Geniez M, Siebel CW, Kim LA, D'Amore PA, Arboleda-Velasquez JF. Therapeutic antibody targeting of Notch3 signaling prevents mural cell loss in CADASIL. J Exp Med. 2017;214:2271–82. PubMed PMID: 28698285.

Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, Powell JF. Diagnostic strategies in CADASIL. Neurology. 2002;59:1134–8. PubMed PMID: 12395806.

Martignetti JA, Tian L, Li D, Ramirez MC, Camacho-Vanegas O, Camacho SC, Guo Y, Zand DJ, Bernstein AM, Masur SK, Kim CE, Otieno FG, Hou C, Abdel-Magid N, Tweddale B, Metry D, Fournet JC, Papp E, McPherson EW, Zabel C, Vaksmann G, Morisot C, Keating B, Sleiman PM, Cleveland JA, Everman DB, Zackai E, Hakonarson H. Mutations in PDGFRB Cause Autosomal-Dominant Infantile Myofibromatosis. Am J Hum Genet. 2013;92:1001–7. PubMed PMID: 23731542.

Meuwissen ME, Halley DJ, Smit LS, Lequin MH, Cobben JM, de Coo R, van Harssel J, Sallevelt S, Woldringh G, van der Knaap MS, de Vries LS, Mancini GM. The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature. Genet Med. 2015;17:843–53. PubMed PMID: 25719457.

Mizuno T, Muranishi M, Torugun T, Tango H, Nagakane Y, Kudeken T, Kawase Y, Kawabe K, Oshima F, Yaoi T, Itoh K, Fushiki S, Nakagawa M. Two Japanese CADASIL families exhibiting Notch3 mutation R75P not involving cysteine residue. Intern Med. 2008;47:2067–72. PubMed PMID: 19043263.

Mizuta I, Watanabe-Hosomi A, Koizumi T, Mukai M, Hamano A, Kondo M, Nakagawa M, Tomimoto H, Hirano T, Uchino M, Onodera O, Mizuno T. New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukocencephalopathy in Japan. J Neurol Sci. 2017;381:62–7. PubMed PMID: 28991717.

Moccia M, Mosca L, Erro R, Cervasio M, Allocca R, Vitale C, Leonardi A, Caranci F, Del Basso-De Caro ML, Barone P, Penco S. Hypomorphic NOTCH3 mutation in an Italian family with CADASIL features. Neurobiol Aging. 2015;36:547.e5–11.

Monet-Leprêtre M, Bardot B, Lemaire B, et al. Distinct phenotypic and functional features of CADASIL mutations in the Notch3 ligand binding domain. Brain. 2009;132:1601–12. PubMed PMID: 19293235.

Monet-Leprêtre M, Haddad I, Baron-Menguy C, Fouillot-Panchal M, Riani M, Domenga-Denier V, Dussaule C, Cognat E, Vinh J, Joutel A. Abnormal recruitment of extracellular matrix proteins by excess Notch3 ECD: a new pathomechanism in CADASIL. Brain. 2013;136:1830–45. PubMed PMID: 23649698.

Moreton FC, Cullen B, Delles C, Santosh C, Gonzalez RL, Dani K, Muir KW. Vasoreactivity in CADASIL: Comparison to structural MRI and neuropsychology. J Cereb Blood Flow Metab. 2018;38:1085–95. PubMed PMID: 28537106.

Morroni M, Marzioni D, Ragno M, Di BP, Cartechini E, Pianese L, Lorenzi T, Castellucci M, Scarpelli M. Role of electron microscopy in the diagnosis of cadasil syndrome: a study of 32 patients. PLoS One. 2013;8:e65482. PubMed PMID: 23799017.

Mukai M, Mizuta I, Ueda A, Nakashima D, Kushimura Y, Noto YI, Ohara T, Itoh K, Ando Y, Mizuno T. A Japanese CADASIL patient with homozygous NOTCH3 p.Arg544Cys mutation confirmed pathologically. J Neurol Sci. 2018;394:38–40. PubMed PMID: 30199759.

Mykkänen K, Savontaus ML, Juvonen V, Sistonen P, Tuisku S, Tuominen S, Penttinen M, Lundkvist J, Viitanen M, Kalimo H, Poyhonen M. Detection of the founder effect in Finnish CADASIL families. Eur J Hum Genet. 2004;12:813–9. PubMed PMID: 15378071.

Nakamura T, Watanabe H, Hirayama M, Inukai A, Kabasawa H, Matsubara M, Mitake S, Nakamura M, Ando Y, Uchino M, Sobue G. CADASIL with NOTCH3 S180C presenting anticipation of onset age and hallucinations. J Neurol Sci. 2005;238:87–91. PubMed PMID: 16111703.

Nannucci S, Rinnoci V, Pracucci G, MacKinnon AD, Pescini F, Adib-Samii P, Bianchi S, Dotti MT, Federico A, Inzitari D, Markus HS, Pantoni L. Location, number and factors associated with cerebral microbleeds in an Italian-British cohort of CADASIL patients. PLoS One. 2018;13:e0190878. PubMed PMID: 29370179.

Narayan SK, Gorman G, Kalaria RN, Ford GA, Chinnery PF. The minimum prevalence of CADASIL in northeast England. Neurology. 2012;78:1025–7. PubMed PMID: 22422895.

Nelis P, Kleffner I, Burg MC, Clemens CR, Alnawaiseh M, Motte J, Marziniak M, Eter N, Alten F. OCT-Angiography reveals reduced vessel density in the deep retinal plexus of CADASIL patients. Sci Rep. 2018;8:8148. PubMed PMID: 29802397.

Nolano M, Provitera V, Donadio V, Caporaso G, Stancanelli A, Califano F, Pianese L, Liguori R, Santoro L, Ragno M. Cutaneous sensory and autonomic denervation in CADASIL. Neurology. 2016;86:1039–44. PubMed PMID: 26873958.

Oberstein SAJ. Diagnostic strategies in CADASIL. Neurology. 2003;60:2020.

Opherk C, Peters N, Herzog J, Luedtke R, Dichgans M. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. Brain. 2004;127:2533–9. PubMed PMID: 15364702.

O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology. 2001;56:628–34. PubMed PMID: 11245715.

Panahi M, Yousefi Mesri N, Samuelsson EB, Coupland KG, Forsell C, Graff C, Tikka S, Winblad B, Viitanen M, Karlström H, Sundström E, Behbahani H. Differences in proliferation rate between CADASIL and control vascular smooth muscle cells are related to increased TGFβ expression. J Cell Mol Med. 2018;22:3016–24. PubMed PMID: 29536621.

Park S, Park B, Koh MK, Joo YH. Case report: bipolar disorder as the first manifestation of CADASIL. BMC Psychiatry. 2014;14:175. PubMed PMID: 24929957.

Park SA, Yang CY, Choi SS, Kim WH. Assessment of cerebral hemodynamics to acetazolamide using brain perfusion SPECT in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Clin Nucl Med. 2011;36:158–9. PubMed PMID: 21220990.

Pescini F, Nannucci S, Bertaccini B, Salvadori E, Bianchi S, Ragno M, Sarti C, Valenti R, Zicari E, Moretti M, Chiti S, Stromillo ML, De SN, Dotti MT, Federico A, Inzitari D, Pantoni L. The Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Scale: a screening tool to select patients for NOTCH3 gene analysis. Stroke. 2012;43:2871–6. PubMed PMID: 22996955.

Peters N, Herzog J, Opherk C, Dichgans M. A two-year clinical follow-up study in 80 CADASIL subjects: progression patterns and implications for clinical trials. Stroke. 2004;35:1603–8. PubMed PMID: 15155961.

Peters N, Holtmannspotter M, Opherk C, Gschwendtner A, Herzog J, Samann P, Dichgans M. Brain volume changes in CADASIL: a serial MRI study in pure subcortical ischemic vascular disease. Neurology. 2006;66:1517–22. PubMed PMID: 16717211.

Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. Arch Neurol. 2005a;62:1091–4. PubMed PMID: 16009764.

Peters N, Opherk C, Danek A, Ballard C, Herzog J, Dichgans M. The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. Am J Psychiatry. 2005b;162:2078–85. PubMed PMID: 16263847.

Pfefferkorn T, von Stuckrad-Barre S, Herzog J, Gasser T, Hamann GF, Dichgans M. Reduced cerebrovascular CO(2) reactivity in CADASIL: A transcranial Doppler sonography study. Stroke. 2001;32:17–21. PubMed PMID: 11136908.

Piccirillo G, Magrì D, Mitra M, Rufa A, Zicari E, Stromillo ML, De Stefano N, Dotti MT. Increased QT variability in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Eur J Neurol. 2008;15:1216–21. PubMed PMID: 18803652.

Pretegiani E, Rosini F, Dotti MT, Bianchi S, Federico A, Rufa A. Visual system involvement in CADASIL. J Stroke Cerebrovasc Dis. 2013;22:1377–84. PubMed PMID: 23635925.

Puy L, De Guio F, Godin O, Duering M, Dichgans M, Chabriat H, Jouvent E. Cerebral Microbleeds and the Risk of Incident Ischemic Stroke in CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy). Stroke. 2017;48:2699–703. PubMed PMID: 28842512.

Ragno M, Berbellini A, Cacchiò G, Manca A, Di Marzio F, Pianese L, De Rosa A, Silvestri S, Scarcella M, De Michele G. Parkinsonism is a late, not rare, feature of CADASIL: a study on Italian patients carrying the R1006C mutation. Stroke. 2013;44:1147–9. PubMed PMID: 23412372.

Ragno M, Trojano L, Pianese L, Boni MV, Silvestri S, Mambelli V, Lorenzi T, Scarpelli M, Morroni M. Renal involvement in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): report of a case with a six-year follow-up. Histol Histopathol. 2012;27:1307–14. PubMed PMID: 22936449.

Razvi SS, Davidson R, Bone I, Muir KW. Is inadequate family history a barrier to diagnosis in CADASIL? Acta Neurol Scand. 2005a;112:323–6. PubMed PMID: 16218915.

Razvi SS, Davidson R, Bone I, Muir KW. The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) in the west of Scotland. J Neurol Neurosurg Psychiatry. 2005b;76:739–41. PubMed PMID: 15834040.

Reyes S, Viswanathan A, Godin O, Dufouil C, Benisty S, Hernandez K, Kurtz A, Jouvent E, O'Sullivan M, Czernecki V, Bousser MG, Dichgans M, Chabriat H. Apathy: a major symptom in CADASIL. Neurology. 2009;72:905–10. PubMed PMID: 19273824.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Roine S, Poyhonen M, Timonen S, Tuisku S, Marttila R, Sulkava R, Kalimo H, Viitanen M. Neurologic symptoms are common during gestation and puerperium in CADASIL. Neurology. 2005;64:1441–3. PubMed PMID: 15851739.

Ruchoux MM, Maurage CA. CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neuropathol Exp Neurol. 1997;56:947–64. PubMed PMID: 9291937.

Rufa A, Guideri F, Acampa M, Cevenini G, Bianchi S, De Stefano N, Stromillo ML, Federico A, Dotti MT. Cardiac autonomic nervous system and risk of arrhythmias in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Stroke. 2007;38:276–80. PubMed PMID: 17218610.

Rutten JW, Boon EM, Liem MK, Dauwerse JG, Pont MJ, Vollebregt E, Maat-Kievit AJ, Ginjaar HB, Lakeman P, van Duinen SG, Terwindt GM, Lesnik Oberstein SA. Hypomorphic NOTCH3 alleles do not cause CADASIL in humans. Hum Mutat. 2013;34:1486–9. PubMed PMID: 24000151.

Rutten JW, Dauwerse HG, Gravesteijn G, van Belzen MJ, van der Grond J, Polke JM, Bernal-Quiros M, Lesnik Oberstein SA. Archetypal NOTCH3 mutations frequent in public exome: implications for CADASIL. Ann Clin Transl Neurol. 2016a;3:844–53. PubMed PMID: 27844030.

Rutten JW, Dauwerse HG, Peters DJ, Goldfarb A, Venselaar H, Haffner C, van Ommen GJ, Aartsma-Rus AM, Lesnik Oberstein SA. Therapeutic NOTCH3 cysteine correction in CADASIL using exon skipping: in vitro proof of concept. Brain. 2016b;139:1123–35. PubMed PMID: 26912635.

Rutten JW, Haan J, Terwindt GM, van Duinen SG, Boon EM, Lesnik Oberstein SA. Interpretation of NOTCH3 mutations in the diagnosis of CADASIL. Expert Rev Mol Diagn. 2014;14:593–603. PubMed PMID: 24844136.

Rutten JW, Van Eijsden BJ, Duering M, Jouvent E, Opherk C, Pantoni L, Federico A, Dichgans M, Markus HS, Chabriat H, Lesnik Oberstein SAJ. The effect of NOTCH3 pathogenic variant position on CADASIL disease severity: NOTCH3 EGFr 1-6 pathogenic variant are associated with a more severe phenotype and lower survival compared with EGFr 7-34 pathogenic variant. Genet Med. 2019;21:676–82. PubMed PMID: 30032161.

Schröder JM, Zuchner S, Dichgans M, Nagy Z, Molnar MJ. Peripheral nerve and skeletal muscle involvement in CADASIL. Acta Neuropathol (Berl). 2005;110:587–99. PubMed PMID: 16328531.

Sicurelli F, Dotti MT, De Stefano N, Malandrini A, Mondelli M, Bianchi S, Federico A. Peripheral neuropathy in CADASIL. J Neurol. 2005;252:1206–9. PubMed PMID: 15827866.

Singhal S, Bevan S, Barrick T, Rich P, Markus HS. The influence of genetic and cardiovascular risk factors on the CADASIL phenotype. Brain. 2004;127:2031–8. PubMed PMID: 15229130.

Singhal S, Rich P, Markus HS. The spatial distribution of MR imaging abnormalities in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and their relationship to age and clinical features. AJNR Am J Neuroradiol. 2005;26:2481–7. PubMed PMID: 16286388.

Soong BW, Liao YC, Tu PH, Tsai PC, Lee IH, Chung CP, Lee YC. A homozygous NOTCH3 mutation p.R544C and a heterozygous TREX1 variant p.C99MfsX3 in a family with hereditary small vessel disease of the brain. J Chin Med Assoc. 2013;76:319–24. PubMed PMID: 23602593.

Sureka J, Jakkani RK. Clinico-radiological spectrum of bilateral temporal lobe hyperintensity: a retrospective review. Br J Radiol. 2012;85:e782–92. PubMed PMID: 22422381.

Tan RYY, Markus HS. CADASIL: Migraine, Encephalopathy, Stroke and Their Inter-Relationships. PLoS One. 2016;11:e0157613. PubMed PMID: 27309730.

Tatsch K, Koch W, Linke R, Poepperl G, Peters N, Holtmannspoetter M, Dichgans M. Cortical hypometabolism and crossed cerebellar diaschisis suggest subcortically induced disconnection in CADASIL: an 18F-FDG PET study. J Nucl Med. 2003;44:862–9. PubMed PMID: 12791811.

Tikka S, Mykkänen K, Ruchoux MM, Bergholm R, Junna M, Poyhonen M, Yki-Jarvinen H, Joutel A, Viitanen M, Baumann M, Kalimo H. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. Brain. 2009;132:933–9. PubMed PMID: 19174371.

Tuominen S, Juvonen V, Amberla K, Jolma T, Rinne JO, Tuisku S, Kurki T, Marttila R, Poyhonen M, Savontaus ML, Viitanen M, Kalimo H. Phenotype of a homozygous CADASIL patient in comparison to 9 age-matched heterozygous patients with the same R133C Notch3 mutation. Stroke. 2001;32:1767–74. PubMed PMID: 11486103.

Tuominen S, Miao Q, Kurki T, Tuisku S, Pöyhönen M, Kalimo H, Viitanen M, Sipilä HT, Bergman J, Rinne JO. Positron emission tomography examination of cerebral blood flow and glucose metabolism in young CADASIL patients. Stroke. 2004;35:1063–7. PubMed PMID: 15017012.

Valenti R, Pescini F, Antonini S, Castellini G, Poggesi A, Bianchi S, Inzitari D, Pallanti S, Pantoni L. Major depression and bipolar disorders in CADASIL: a study using the DSM-IV semi-structured interview. Acta Neurol Scand. 2011;124:390–5. PubMed PMID: 21428968.

van den Boom R, Lesnik Oberstein SA, Ferrari MD, Haan J, van Buchem MA. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR imaging findings at different ages--3rd-6th decades. Radiology. 2003;229:683–90. PubMed PMID: 14593195.

van Den Boom R, Lesnik Oberstein SA, van Duinen SG, Bornebroek M, Ferrari MD, Haan J, van Buchem MA. Subcortical lacunar lesions: an MR imaging finding in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Radiology. 2002;224:791–6. PubMed PMID: 12202716.

Vinciguerra C, Rufa A, Bianchi S, Sperduto A, De Santis M, Malandrini A, Dotti MT, Federico A. Homozygosity and severity of phenotypic presentation in a CADASIL family. Neurol Sci. 2014;35:91–3. PubMed PMID: 24277202.

Viitanen M, Sundström E, Baumann M, Poyhonen M, Tikka S, Behbahani H. Experimental studies of mitochondrial function in CADASIL vascular smooth muscle cells. Exp Cell Res. 2013;319:134–43. PubMed PMID: 23036509.

Wang Z, Yuan Y, Zhang W, Lv H, Hong D, Chen B, Liu Y, Luan X, Xie S, Wu S. NOTCH3 mutations and clinical features in 33 mainland Chinese families with CADASIL. J Neurol Neurosurg Psychiatry. 2011;82:534–9. PubMed PMID: 20935329.

Weller M, Dichgans J, Klockgether T. Acetazolamide-responsive migraine in CADASIL. Neurology. 1998;50:1505.

Williamson EE, Chukwudelunzu FE, Meschia JF, Witte RJ, Dickson DW, Cohen MD. Distinguishing primary angiitis of the central nervous system from cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: the importance of family history. Arthritis Rheum. 1999;42:2243–8. PubMed PMID: 10524700.

Wollenweber FA, Hanecker P, Bayer-Karpinska A, Malik R, Bäzner H, Moreton F, Muir KW, Müller S, Giese A, Opherk C, Dichgans M, Haffner C, Duering M. Cysteine-sparing CADASIL mutations in NOTCH3 show proaggregatory properties in vitro. Stroke. 2015;46:786–92. PubMed PMID: 25604251.

Yao M, Herve D, Jouvent E, Duering M, Reyes S, Godin O, Guichard JP, Dichgans M, Chabriat H. Dilated perivascular spaces in small-vessel disease: a study in CADASIL. Cerebrovasc Dis. 2014;37:155–63. PubMed PMID: 24503815.

Yin X, Wu D, Wan J, Yan S, Lou M, Zhao G, Zhang B. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: phenotypic and mutational spectrum in patients from mainland China. Int J Neurosci. 2015;125:585–92. PubMed PMID: 25105908.

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