

## Case Report

# A Novel Heterozygous Variant in Exon 19 of NOTCH3 in a Saudi Family with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

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Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL; OMIM #[125310](#)) is the most common cause of monogenic familial cerebral small vessel disease. It typically manifests at middle adulthood with highly variable clinical features including migraine with aura, recurrent transient ischemic attacks or ischemic strokes, mood disorders, and progressive cognitive decline. It is caused by mutations in the *NOTCH3* gene, which maps to the short arm of chromosome 19 and encode for epidermal growth factor-like repeats. In this article, we report a 40-year-old male patient who presented with a two-year history of progressive cognitive decline including impaired attention, memory, executive functions, and processing speed whose family history was strongly positive for young-onset ischemic stroke and memory impairment. His father, uncle, and grandfather died due to ischemic strokes and cognitive impairment (similar condition). A whole exome sequencing to the patient (proband II-1) revealed a novel heterozygous missense variant c.3009G>T, p.(Trp1003Cys) (chr19:15291625; hg19) in exon 19 of the *NOTCH3* gene. Sanger sequencing was used to confirm the variant in other family members. This variant has not been described in the literature so far. The novel mutation described in the present study widened the genetic spectrum of *NOTCH3*-associated diseases, which will benefit studies addressing this disease in the future. CADASIL remains a disabling disorder leading to medical retirement in our patient due to late clinical presentation, lack of family history taking prior to joining the military, and lack of curative therapy. Further research for therapeutic options is needed including stem cell therapy.

**Key Words:** *NOTCH3*—Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy—CADASIL—Novel Mutation—Saudi Arabia

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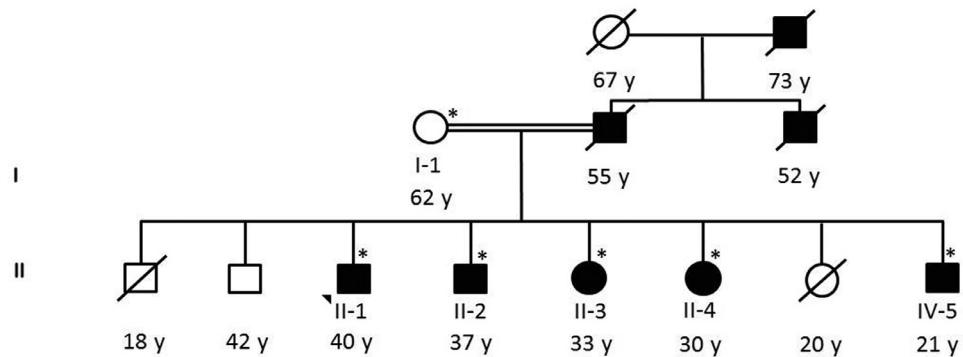
## Introduction

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL; OMIM #125310) is the most common cause of monogenic familial cerebral small vessel disease.<sup>1</sup> It typically manifests at middle adulthood with highly variable clinical features including migraine with aura, recurrent transient ischemic attacks or ischemic strokes, mood disorders, and progressive cognitive decline.<sup>2</sup> The primary pathogenesis of CADASIL is mutations in the *NOTCH3* gene on chromosome 19p13.2–p13.1. The human *NOTCH3* gene is made up of 34 exons, which encode a transmembrane receptor found in smooth muscle cells of systemic and intracranial arteries.<sup>3</sup> Over 98% of CADASIL patients have a distinctive missense mutation in one of *NOTCH3* exons 2–24, leading to a gain or loss of a cysteine residue in one of the epidermal growth factor-like repeats located in the extracellular domain of the *NOTCH3* protein.<sup>4</sup> Previous studies have reported stereotypical CADASIL missense mutations in exons 3,4,8,11,15,18,20,25, and 28.<sup>5</sup> Moreover, variations have been found in *NOTCH3* mutations according to ethnicity. Mutations in exons 4 and 3 were the most common sites of mutation in Caucasian and mainland Chinese populations, while mutations in exon 11 were most common in Korean and Taiwanese populations.<sup>6</sup> In this article, we report a Saudi family with CADASIL caused by a heterozygous variant in exon 19 of the *NOTCH3* gene. In addition, we are reviewing previous studies originating from Saudi Arabia and review the topic.

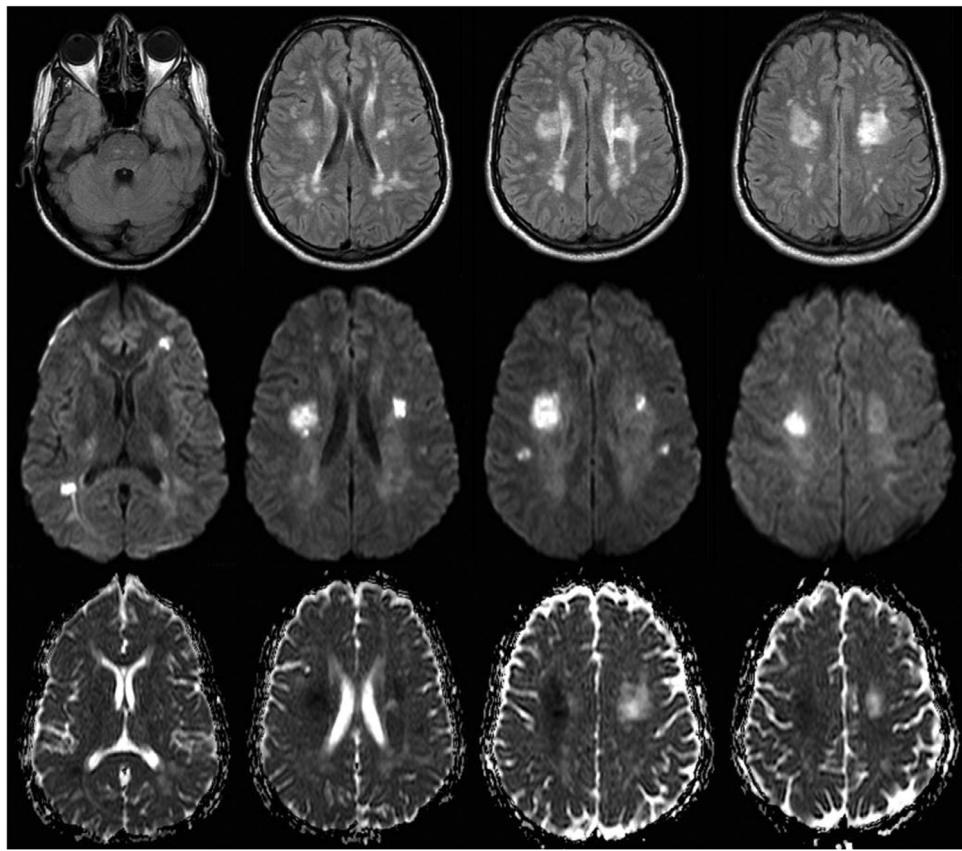
## Case report

The proband is a 40-year-old male patient who presented with a two-year history of progressive cognitive decline including impaired attention, memory, executive functions, and processing speed. In addition, he had difficulty walking, urinary urgency, and recurrent attacks of migraine with aura. He worked as a soldier and was sent to the neurology clinic for assessment regarding his ability to perform military work and whether medical retirement

is recommended. His past medical history was significant for dyslipidemia with no past medical history of cerebrovascular diseases, trauma, or exposure to drugs or toxins. He did not smoke and never drank alcohol. His family history was strongly positive for young-onset ischemic stroke and memory impairment. His father, uncle, and grandfather died due to ischemic strokes and cognitive impairment (similar condition). His mother is still alive and healthy. His oldest brother died at the age of 18 years due to car accident, and one younger sister died at the age of 20 years due to another medical condition. He had another older brother who is healthy but refused to volunteer blood for genetic testing. All his younger living siblings are symptomatic but to a lesser degree (Fig. 1). The patient had no risk factors for stroke apart from dyslipidemia. Clinically, the patient did not perform well on mini-mental status examination and Montreal cognitive assessment<sup>7</sup> and scored 21/30 and 22/30, respectively. Motor examination showed hyperreflexia, increased tone in the lower extremities, and bilateral Babinski sign. His gait and stance were impaired due to spastic legs and incoordination. Cerebellar examination showed dysdiadochokinesia and difficulty performing tandem gait. His routine basic biochemical and hematological screen was unremarkable. He had a magnetic resonance imaging (MRI) of the brain, which demonstrated multiple scattered subcortical and periventricular white matter T2 and fluid-attenuated inversion recovery bright signal intensity lesions, which are symmetrically distributed. Within the white matter, the frontal and temporal lobes were the sites with the highest lesion load. Some of the lesions demonstrated diffusion restriction (Fig. 2). Workup for other possible causes for the patient's presentation including central nervous system vasculitis, connective tissue diseases, cardiac emboli, and drug and substance abuse were all unremarkable. Furthermore, genetic testing was performed to the patient (proband II-1) using whole exome sequencing after acquiring informed consent. Sequence analysis identified a heterozygous missense variant c.3009G>T, p.(Trp1003Cys) (chr19:15291625; hg19) in exon 19 of the *NOTCH3* gene. To the best of our knowledge, this variant



**Figure 1.** Family pedigree showing the details of the members of the family. The samples marked with asterisks were available for genetic testing. Arrowhead indicates the proband included in this study.



**Figure 2.** MRI of the brain showing multiple scattered subcortical and periventricular white matter bright signal intensity lesions, which are symmetrically distributed. Within the white matter, the frontal and temporal lobes were the sites with the highest lesion load. Some of the lesions demonstrated diffusion restriction. The sequences included fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC).

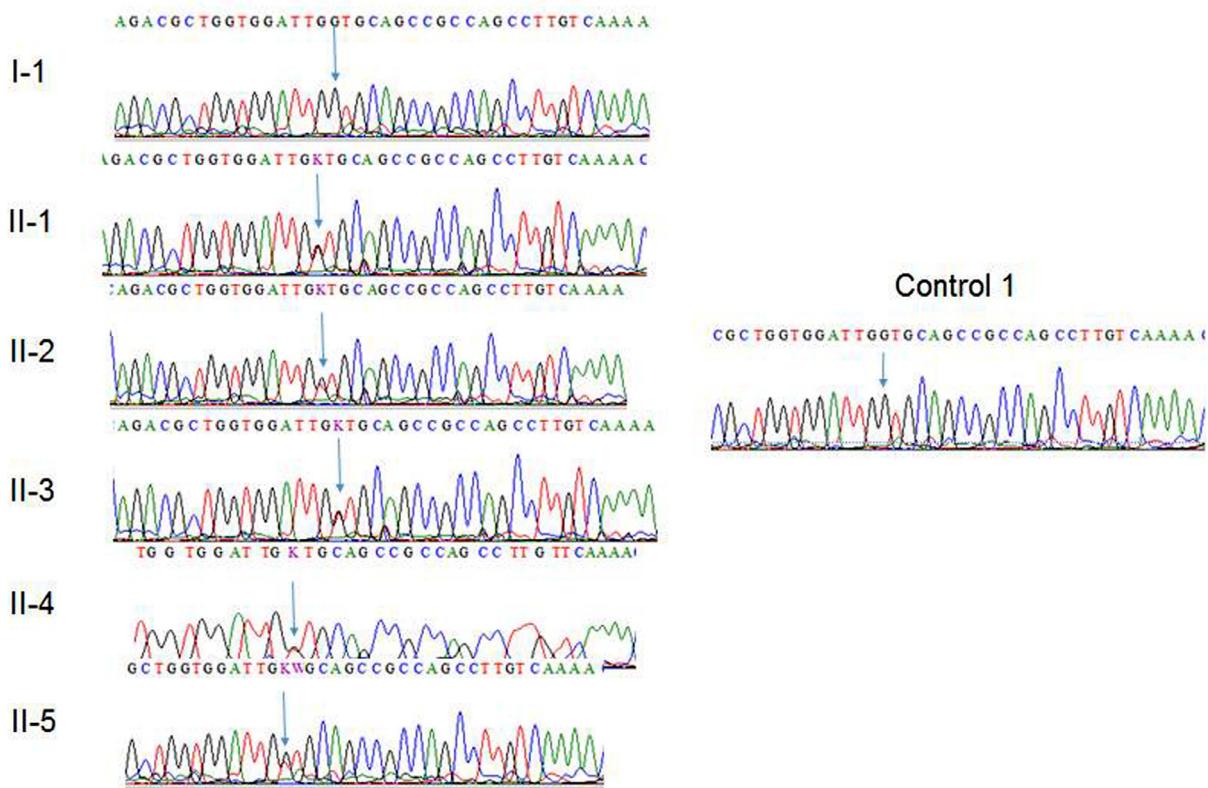
has not been described in the literature so far. Allele frequencies in the general population have not been documented. The variant identified in the proband is predicted to be pathogenic by 7 of 10 bioinformatics tools used (SIFT, MutationTaster, PloyP, PolyPhen2, GERP, SiPhy, and CADD version v1.4). Sanger sequencing was used to confirm the variant in other family members (Fig. 3). The patient was treated with aspirin, cholesterol-lowering agents, mood stabilizers, and selective serotonin reuptake inhibitor. Genetic counseling was done, and the patient was sent for early medical retirement.

## Discussion

CADASIL is an autosomal dominant small vessel disease and considered the most common form of adult-onset hereditary vasculopathy. It causes lacunar ischemic infarcts with resultant subcortical dementia, migraine, encephalopathy, and psychiatric disturbances.<sup>8</sup> The onset of recurrent subcortical ischemic events is usually around 49 years of age (range 20–70 years). Stroke typically occurs irrespective of cardiovascular risk factors, and ischemic events tend to recur throughout the patient's life. However, after the age of 60, the deficits may become

heterogeneous.<sup>9</sup> The disease is progressive with variability in clinical features even in patients within the same family.<sup>10</sup>

CADASIL should be suspected in patients who present with ischemic strokes in the young who suffer from cognitive impairment with a strong family history of a similar condition.<sup>11</sup> CADASIL has a somewhat characteristic appearance in neuroimaging, and a radiologist may suggest a diagnosis when reporting MRI images.<sup>12</sup> These abnormalities include T2-weighted prominent symmetric white matter hyperintense lesions involving the anterior pole of the temporal lobes, paramedian superior frontal subcortical white matter, and/or external capsules. In addition, lacunar or subcortical infarcts can occur manifesting as foci of restricted diffusion on diffusion-weighted imaging (bright) and apparent diffusion coefficient (dark) sequences typically measuring 1–1.5 cm. Microbleeds are also observed in T2\*-gradient echo MRI sequences seen as multiple punctate foci of susceptibility-hypointensity.<sup>13</sup> In rare cases, the characteristic temporal pole lesions may be absent, especially in the Asian population. The involvement of the anterior temporal pole on MRI has sensitivity of 89% and specificity of 86% in diagnosing CADASIL.<sup>14</sup> What appears unique in our case is that there was no temporal pole involvement.



**Figure 3.** Representative chromatograph of NOTCH3 Sanger sequencing read of the available family members. Genetic analysis identified this variant in the proband and all affected brothers and sisters that were included in the analysis.

The diagnosis of CADASIL is established either by genetic testing or the detection of characteristic findings in a skin biopsy. Electron microscopy of skin biopsies may reveal deposits of granular osmophilic material, a pathological hallmark of CADASIL, within the basal membranes of vascular smooth muscle cells.<sup>15</sup>

CADASIL cases have been reported worldwide including Europe, the Americas, Japan, Turkey, South Africa, and Tanzania. Two families with CADASIL have been previously reported from Saudi Arabia.<sup>16–17</sup> To the best of our knowledge, this is the third Saudi family with CADASIL settled in the western region of the Arabian peninsula. Here, we described the clinical and genetic findings and reported a novel mutation in exon 19 of the NOTCH3 gene. Although upon reviewing the literature, those with epidermal growth factor-like repeats mutations in domains 9 through 34 tend to have less symptomatology and a later onset, this was not found in our patient's family. The onset was earlier and the disease was severe.

No agents have been proven to be beneficial in patients with CADASIL in terms of treatment and stroke prevention, including antiplatelets, homocysteine-lowering agents, anti-hypertensives, and cholesterol-lowering agents. Thus, leaving only standard supportive care targeted at the symptoms. Identifying the underlying variants of genetic mutations leading to CADASIL may provide a better insight into the

pathways of the disease and help in the future discovery of specific novel drug targets.<sup>18</sup>

## Conclusion

In conclusion, we describe a novel heterozygous missense variant c.3009G > T, p.(Trp1003Cys) (chr19:15291625; hg19) in exon 19 of the NOTCH3 gene in a Saudi family. This variant has not been described in the literature so far. The novel mutation described in the present study widened the genetic spectrum of NOTCH3-associated diseases, which will benefit studies addressing this disease in the future. CADASIL remains a disabling disorder leading to medical retirement in our patient due to late clinical presentation, lack of family history taking prior to joining the military, and lack of curative therapy. Further research for therapeutic options is needed including stem cell therapy.

## Declaration Competing of Interest

The authors declare that they have no conflicts of interest.

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