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NOTCH3 C201R variant causes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) that can be confused with early-onset Alzheimer's disease

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Abstract

Background: *NOTCH3* is the causative gene for autosomal dominant cerebral arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL) which is associated with both stroke and dementia. When CADASIL presents primarily as dementia it can be difficult to distinguish from Alzheimer's disease (AD) at both the clinical and neuropathological levels.

Methods: We performed exome sequencing of several affected individuals from a large family affected with AD. PCR amplification and direct Sanger sequencing were used to verify variants detected by exome analysis and to screen family members at-risk to carry those variants. Neuropathologic brain evaluation by immunohistochemistry and MRI were performed for the carriers of the NOTCH3 variant.

Results: In a three-generation family with AD, we found a c.601 T > C p.Cys201Arg variant in the *NOTCH3* gene that caused clinical and neuropathological manifestations of CADASIL. These features included earlier onset of dementia accompanied by behavioral abnormalities in the father and son and white matter abnormalities in the asymptomatic grandson. The family is one branch of a large pedigree studied by the Alzheimer's Disease Sequencing Project (ADSP). As part of the

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Authors contribution

O.K., M.O.D., D.T., S.J., W.H.R., T.D.B., – conception and design of the study, T.D.B., D.T., S.J. - sample acquisition and ascertainment, O.K., R.A.Y., A.N., M.O.D. – acquisition of data, O.K., D.T., S.J., W.H.R., T.D.B. - funding acquisition, O.K., S.A.B., M.O.D. - analysis and interpretation of data, O.K., R.A.Y., T.D.B. – drafting the manuscript, O.K., D.T., S.J., W.H.R., T.D.B., – revising the manuscript.

ADSP linkage analysis and whole genome sequencing endeavor, an ABCA1 variant, p.Ala937Val, was previously found associated with AD in this pedigree.

Conclusions: Our findings, together with other reported pathogenic missense variants of the C201 codon in NOTCH3, support the role of cysteine 201 as a mutation hotspot for CADASIL and highlight the genetic complexity both clinically and pathologically of AD and related dementia.

Keywords

Vascular dementia; Exome sequencing; Mutation hotspot

1. Introduction

Vascular pathology is an important contributor to cognitive decline and dementia in the elderly; over half of patients diagnosed with Alzheimer's disease (AD) also present with cerebrovascular pathology [1]. Rare pathogenic variants in the NOTCH3 receptor are responsible for autosomal dominant cerebral arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL), a progressive neurovascular condition manifested by recurrent strokes, cognitive decline, and psychiatric disturbance. The majority of deleterious missense *NOTCH3* variants found in CADASIL patients destabilize the protein by changing the number of cysteine residues in EGF-like repeats. *NOTCH3* variants are also associated with increased risk of stroke and vascular dementia [2–4].

The contribution of *NOTCH3* variants to AD risk is not well established, particularly its role in "mixed" type of dementia, in which amyloid/tau and cerebrovascular pathologies co-occur. Herein, we performed exome analysis of additional members of a multi-generation AD family that was part of the Alzheimer's Disease Sequencing Project (ADSP). The family is of Volga German ethnic background and does not have the AD-causative PSEN2 variant reported in that population [5–7]. By genome sequencing in this family, the ADSP identified a pathogenic variant in the ATP binding cassette subfamily A member 1 (*ABCA1*) [8], a gene physiologically linked to APOE function [9,10]. A rare missense *ABCA1* variant, c.2810C > T (p.Ala937Val; rs137854495), segregated with dementia in four individuals from three branches of the family (family-specific LOD = 2.04). Several members of the family had early onset of dementia in the absence of an *APOE4* ε4 allele, suggesting additional risk genes. As more family members became available for genetic studies, we performed whole exome sequencing and targeted genotyping and searched for pathogenic variants in genes known to be involved in neurologic disorders. We found a pathogenic variant in the *NOTCH3* gene that was transmitted in three generations of one branch of the family and confirmed CADASIL pathology in the carriers.

2. Methods

2.1. Patients

The family (Fig. 1) was ascertained as part of a long-standing effort to evaluate and sample multiplex families with Alzheimer's disease. Subjects provided informed consent under protocols approved by the University of Washington Institutional Review Board.

2.2. DNA isolation, PCR and exome sequencing

Genomic DNA was extracted from the peripheral blood and brain tissue using PureLink Genomic DNA kit, ThermoFisher, and DNAeasy Blood and Tissue kit, Qiagen. Whole-exome sequencing was performed using SeqCap EZ Human Exome Library v3.0 (Roche NimbleGen; Madison, WI) capture and an Illumina (San Diego, CA) HiSeq 1000 system with paired-end 100 bp reads [11]. PCR amplification and direct Sanger sequencing were used to verify the variants detected by exome and screen family members in generations II-IV. Primers used for amplification were: Forward 5′-TAGGGCTCACTCACCAGGAA-3′ and Reverse 5′-TCAACACACCTGGCTCCTTC-3′.

2.3. Postmortem neuropathologic examination, immunohistochemistry, and special stains

Informed consent for research brain donation was obtained from the legal next of kin according to protocols approved by the University of Washington Institutional Review Board. Neuropathologic brain evaluation was performed for subjects III-1 and IV-1. In each case, the entire brain was fixed in 10% neutral buffered formalin. The fixed brain was transected through the midbrain before being sectioned at 4-millimeter intervals (coronal for the cerebrum, transverse for the posterior fossa). Due to the differing years of collection, complete standard sections following the current National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria for evaluation of AD [12,13] were taken for the brain of subject IV-1 only. However, in both cases, representative samples were taken from the cerebral cortex, hippocampi, deep gray nuclei, midbrain, brainstem, and cerebellum, with additional sections relevant to the gross pathology. Slides with 5 μm-thick sections of formalin-fixed, paraffin-embedded (FFPE) tissue were stained with hematoxylin and eosin/Luxol fast blue (H&E/LFB), with a subset immunohistochemically stained per the NIA-AA protocol [12]. Antibody targets included amyloid β (clone 6E10; Biolegend; 1:1000), hyperphosphorylated tau (clone AT8; Invitrogen; 1:1000), and α-synuclein (clone LB509; Invitrogen; 1:200). A Bielschowsky silver stain was manually performed on 8 μm sections from multiple cortical regions. Sections of the frontal cortex were also stained for Periodic acid–Schiff (PAS), and monoclonal NOTCH3 antibody (clone 1E4; Millipore; 1:2000).

3. Results

3.1. A c.601 T > C p.Cys201Arg variant in NOTCH3 in a patient with early onset of dementia

We searched whole exome sequences of three family members (Fig. 1) for potentially damaging variants in genes associated with CNS pathologies. A c.601 T > C p.Cys201Arg in *NOTCH3* was identified in the index patient, III-1. The variant was transmitted to his son, IV-1, and grandson (V-1). The Cys201Arg alteration has a high pathogenicity score (CADD = 24.4) and is predicted to be "probably damaging" by PolyPhen and "deleterious" by SIFT. Cysteine 201 resides in the EGF-like repeat 5, one of the first six repeats that are most frequently mutated in CADASIL patients. The c.601 T > C p.Cys201Arg variant was previously reported in two CADASIL patients of different ethnic background [14,15]. Other changes at the same cysteine residue were reported in a patient with CADASIL (p.Cys201Tyr [16]) and in patients with subcortical vascular dementia (p.Cys201Phe and

p.Cys201Ser, [4]) affirming that cysteine 201 alterations are pathogenic. Variants affecting cysteine 201 are exceedingly rare in the general population (absent from more than 150,000 individuals in gnomAD).

3.2. Genotype-phenotype correlations

The index case III-1 was a college-educated engineer who had a job demotion at age 55 because of poor performance. He was required to retire at age 59 and was noted to have mild memory loss which was slowly progressive. At age 71 a small stroke caused dysarthria, drooling and right facial weakness. By age 79 he was clearly demented with episodic aggressive behavior and was admitted to a nursing home. Examination showed poor short-term memory, disorientation to place and time, inability to recognize family members, vocalization of nonsense sentences, unsteady gait, and hyperactive tendon reflexes with no focal neurologic deficits. The clinical diagnosis was AD with an element of multi-infarct dementia. He died at age 81.

At the time of neuropathologic examination, the whole brain weighed 1470 g fresh, 1587 g fixed, and was without atherosclerosis. Microscopic examination revealed AD neuropathological change to be high, with a combination of moderate neuritic plaques by CERAD criteria, BRAAK stage V neurofibrillary tangle distribution, and Thal phase 4 amyloid plaque distribution [13]. The high AD neuropathologic change was considered an adequate explanation of cognitive impairment or dementia. In addition, there was evidence of vascular pathology (Fig. 2 A–D). Chronic macroinfarcts were identified in the left cingulum, striatum, centrum semiovale, medial frontal gyrus, and cerebellar cortex. Patchy white matter disease was also present, most prominent in the subcortical white matter. The white matter changes were largely characterized by mild myelin pallor and gliosis, with occasional foci also demonstrating tissue rarefaction with scattered axonal spheroids. At the time of death (1993, prior to the recognition of CADASIL as a distinct entity) the final neuropathologic diagnosis was AD with additional microinfarcts. More than 25 years later his son (IV-1) died with dementia and his brain autopsy revealed CADASIL. Therefore, III-1's brain tissue was reexamined, and small arteries and arterioles demonstrated mural thickening and intramural granular deposits which were positive for PAS and NOTCH3. Thus, the new combined findings were consistent with a diagnosis of both AD and CADASIL. Finally, alpha synuclein-positive Lewy bodies and neurites were identified in the brainstem, amygdala, cingulate cortex, and neocortex, consistent with neocortical (diffuse) Lewy body disease pathology [17].

Individual IV-1, also a college-educated engineer, was imprisoned at age 62 for antisocial inappropriate felony-level behavior. At age 70, he began to exhibit behavioral changes of apathy, social withdrawal, confusion, poor personal hygiene, and restricted speech that progressively worsened and included memory loss. He did not have a clinical history of stroke. He died of pneumonia at age 78. At the time of neuropathologic examination, the whole brain weighed 1435 g fresh, 1532 g fixed, and showed severe atherosclerosis on external examination. Cut sections of the brain demonstrated numerous discolored, cavitary lesions, largely concentrated in the subcortical white matter of all lobes. Microscopic examination revealed extensive white matter disease and chronic

vascular brain injury ranging from numerous micro- and macro-infarcts to diffuse white matter rarefaction, formation of axonal spheroids, and loss of axons. Small arteries and arterioles demonstrated prominent vessel wall thickening with deposition of PAS-positive and NOTCH3-immunoreactive granules (Fig. 2 E–H). The findings were consistent with CADASIL, with more severe and more widespread changes compared to those of III-1. The observed AD-associated neuropathological changes (CERAD sparse neuritic plaque frequency; BRAAK stage III neurofibrillary tangle distribution; Thal phase 1 amyloid plaque distribution) were low and considered an insufficient explanation of cognitive impairment [13]. Lewy bodies were not identified.

At 49 years old, his son, V-1, is currently asymptomatic. However, a brain MRI revealed marked periventricular and subcortical white matter changes indicating significant small vessel pathology (Fig. 3) and consistent with typical pathologies observed in CADASIL/subcortical vascular dementia. As defined by isointense lesions on FLAIR sequence, there were no clear lacunar infarcts. The relatively small size of the temporal lobe lesion likely reflects the preclinical stage of the inherited disease.

4. Discussion

This family is important for two reasons. First, it provides strong evidence that alteration at cysteine 201 in NOTCH3 is pathogenic for dementia. Second, it demonstrates that CADASIL can be confused with AD both clinically (as in IV-1) and pathologically (as in III-1).

The c.601 T > C p.Cys201Arg variant co-segregated with dementia and/or typical MRI manifestations in father, son, and grandson. The same nucleotide variant was previously reported in a CADASIL patient from a Turkish family with a history of early-onset dementia, recurrent strokes, stroke-like episodes and typical MRI manifestations [14], and in an Italian proband from northern Italy [15]. The independent appearance of c.601 T > C p.Cys201Arg on three ethnic backgrounds (Turkish, Italian and Volga-German), as well as pathogenic p.Cys201Phe and p. Cys201Ser changes in the Chinese population [4], confirms that cysteine 201 is a mutation hot spot for CADASIL and vascular dementia.

Because of the frequent co-occurrence of amyloid/tau deposition and cerebrovascular lesions in AD patients, the contribution of cerebrovascular disease risk genes, such as *NOTCH3*, to AD and other types of dementia has been the focus of numerous genetic studies. A population-based study found pathogenic *NOTCH3* variants associated with risk of vascular dementia, stroke, and epilepsy but not with all-cause dementia, sporadic AD or AD/dementia with familial history [3]. An independent study in the Chinese population found a spectrum of cysteine mutations in patients with subcortical vascular dementia, but no pathogenic or likely pathogenic *NOTCH3* variants were found in AD patients [4]. Focusing on exceedingly rare, high impact variants in genes responsible for neurological disorders in the ADSP dataset (whose effects cannot be captured by genome-wide association studies) *NOTCH3* p.Ala284Thr (rs149307620) was identified in ten patients with AD but not in controls [18]. p.Ala284Thr is located in the IGF-like 7 domain and is distinct from cysteine-altering CADASIL and stroke risk variants. In addition, p. Ala284Thr carriers with AD did

not have earlier disease onset characteristic of CADASIL nor did they have a history of strokes. Protein modeling showed that p.Ala284Thr affects NOTCH3 function by changing its interaction with its ligand, JAG1, in contrast to the protein destabilization effect of cysteine mutations.

Interestingly, population-based studies using ExAC samples and UK Biobank whole-exome sequencing data [3,19] found that cumulative frequency of cysteine changes in NOTCH3 IGF-like domains associated with the risk of stroke and vascular dementia exceeded by at least 100 times the prevalence of those known to cause clinical CADASIL disease (2 to 5 of 100,000). This implies that a significant proportion of cysteine-altering *NOTCH3* variants present in the population carry a risk of cerebrovascular pathology but do not produce a clinically recognizable CADASIL phenotype. They may occasionally coincide with more prevalent AD, without being associated with it.

Even though CADASIL (NOTCH3 p.Cys201Arg) combined with AD was responsible for early onset of dementia in III-1 and the severe progressive behavioral phenotype in his son, early onset of dementia in other members without the variant, such as IV-4, suggests presence of additional risk genes in this family. One of those risk genes appears to be *ABCA1*. The confounded genetic burden in this family highlights the complex landscape of AD that in most cases cannot be attributed to a single risk factor.

Acknowledgments

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Abbreviation:

(AD)	Alzheimer's disease
(CADASIL)	cerebral arteriopathy with subcortical infarctions and leukoencephalopathy
(EGF)	epidermal growth factor - like domains
(ADSP)	Alzheimer's Disease Sequencing Project
(ABCA1)	ATP binding cassette subfamily A member 1
(LOD)	linkage odd ratio
(FFPE)	formalin-fixed, paraffin-embedded
(CADD)	Combined Annotation Dependent Depletionscore
(CERAD)	Consortium to Establish a Registry for Alzheimer's Disease score.

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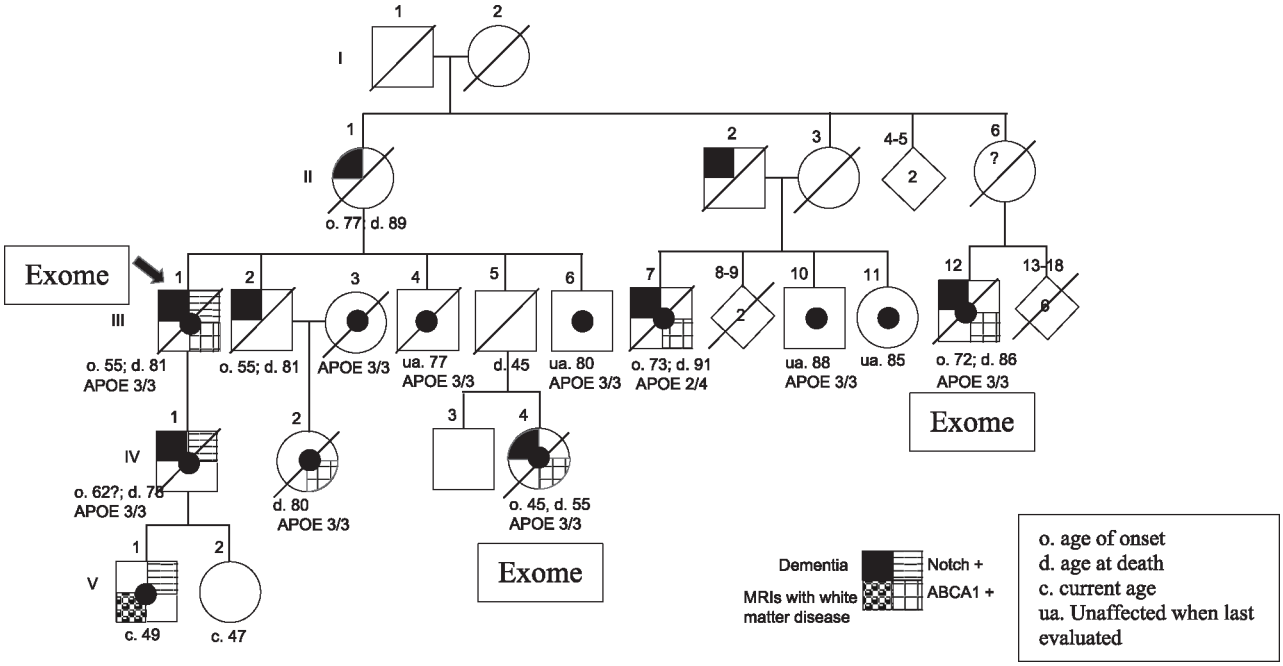

Fig. 1.

Family with Alzheimer's disease and CADASIL. Squares represent males, circles - females; filled black - dementia; NOTCH3+ − c.601 T > C p.Cys201Arg variant in *NOTCH3*; ABCA1+ − c.2810C > T p.Ala937Val variant in *ABCA1*. Exome sequencing was done for individuals III-1, III-12, and IV-4.

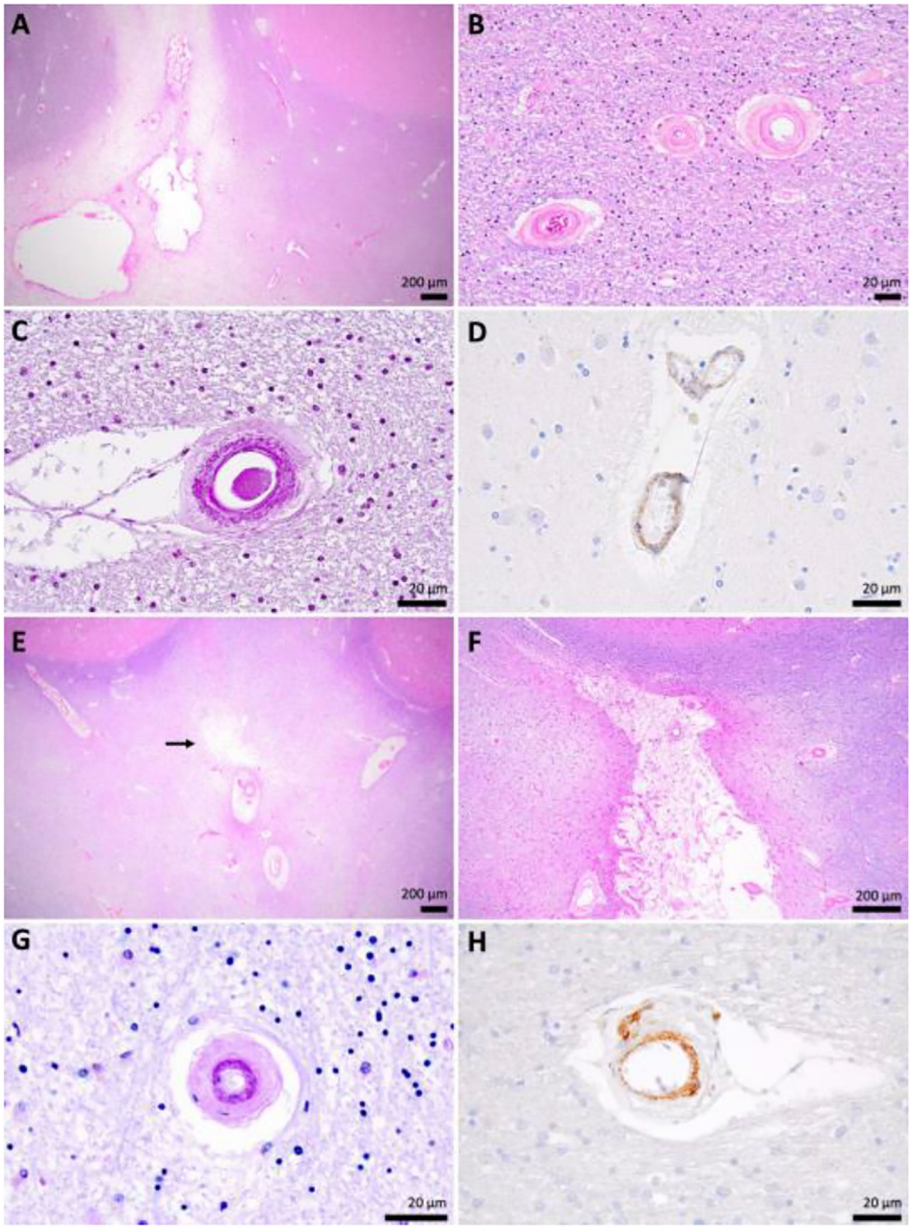

Fig. 2.

Microscopic vascular pathology and features of CADASIL for III-1 [A-D] and IV-1 [*E*-H]. H&E/LFB-stained sections demonstrated a spectrum of cerebrovascular pathology, including a cystic macroinfarct in frontal subcortical white matter [A], as well as scattered small arteries with thickened hyalinized walls within temporal subcortical white matter showing myelin pallor [B]. The thickened vessels contain intramural granular deposits highlighted by PAS stain [C] and positive for NOTCH3 by immunohistochemistry [D]. In contrast, the vascular pathology and associated white matter disease was more severe throughout the brain of IV-1, with representative H&E/LFB-stained left parietal sections demonstrating a spectrum of pathology ranging from prominent subcortical white matter pallor, widened perivascular spaces, thickened vessels, microinfarct formation (arrow) [E], as well as

macroinfarct formation [F]. Thickened, small-caliber arteries within the subcortical white matter show similar intramural granular deposits, highlighted by PAS stain [G] and NOTCH3 immunostaining [H].

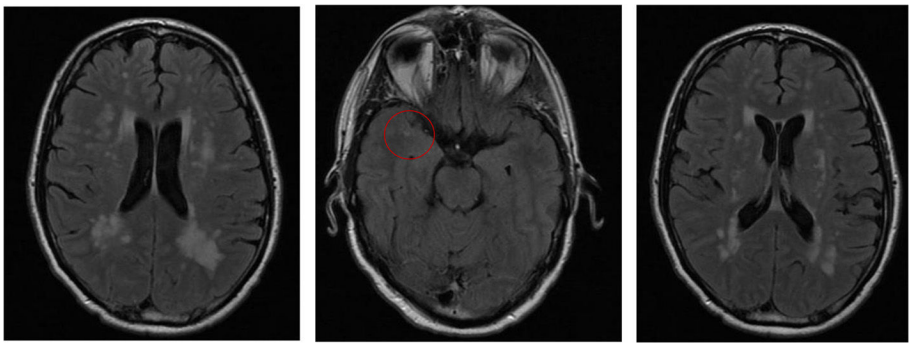

Fig. 3.

Brain MRI of individual V-1 reveals periventricular and subcortical white matter abnormalities. Shown are axial flair images; red circle - an area of hyperintensity at the anterior temporal lobe that is typical of CADASIL. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)