

# Early-Onset Cerebral Amyloid Angiopathy and Alzheimer Disease Related to an APP Locus Triplication

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*Neurol Genet* 2021;7:e609. doi:10.1212/NXG.0000000000000609

## Abstract

### Background and Objective

To report a triplication of the amyloid- $\beta$  precursor protein (*APP*) locus along with relative messenger RNA (mRNA) expression in a family with autosomal dominant early-onset cerebral amyloid angiopathy (CAA) and Alzheimer disease (AD).

### Methods

Four copies of the *APP* gene were identified by quantitative multiplex PCR of short fluorescent fragments, fluorescent in situ hybridization (FISH), and array comparative genomic hybridization. *APP* mRNA levels were assessed using reverse-transcription–digital droplet PCR in the proband's whole blood and compared with 10 controls and 9 *APP* duplication carriers.

### Results

Beginning at age 39 years, the proband developed severe episodic memory deficits with a CSF biomarker profile typical of AD and multiple lobar microbleeds in the posterior regions on brain MRI. His father had seizures and recurrent cerebral hemorrhage since the age of 37 years. His cerebral biopsy showed abundant perivascular amyloid deposits, leading to a diagnosis of CAA. In the proband, we identified 4 copies of a 506-kb region located on chromosome 21q21.3 and encompassing the whole *APP* gene without any other gene. FISH suggested that the genotype of the proband was 3 copies/1 copy corresponding to an *APP* locus triplication, which was consistent with the presence of 2 *APP* copies in the healthy mother and with the paternal medical history. Analysis of the *APP* mRNA level showed a 2-fold increase in the proband and a 1.8 fold increase in *APP* duplication carriers compared with controls.

### Discussion

Increased copy number of *APP* is sufficient to cause AD and CAA, with likely earlier onset in case of triplication compared with duplication.

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## Glossary

**aCGH** = array comparative genomic hybridization; **AD** = Alzheimer disease; **APP** = amyloid- $\beta$  precursor protein; **CAA** = cerebral amyloid angiopathy; **EOAD** = early-onset Alzheimer disease; **MMSE** = Mini Mental State Examination; **mRNA** = messenger RNA; **QMPSF** = quantitative multiplex PCR of short fluorescent fragments.

Amyloid- $\beta$  precursor protein (*APP*) is the main gene known to be involved in autosomal dominantly inherited cerebral amyloid angiopathy (CAA). After the description of point mutations, *APP* locus duplications were identified in 2006 as a cause of early-onset CAA and/or early onset Alzheimer disease (EOAD, onset before 65 years).<sup>1</sup> Such copy number variations encompass at least the *APP* gene, with or without surrounding genes on chromosome 21,<sup>2</sup> and are associated with  $\sim 1.5$ -fold increased messenger RNA (mRNA) levels in blood compared with healthy controls, in similar ranges to patients with trisomy 21.<sup>3</sup> The size of the duplication and the gene content—beyond the critical *APP* gene—do not appear to influence phenotypic presentation in cases.<sup>1,4-6</sup> Patients with trisomy 21 usually show cognitive impairment similar to Alzheimer disease (AD), although they less frequently exhibit cerebral hematoma, suggesting the presence of protective mechanisms in patients with Down syndrome.<sup>7</sup> Indeed, a recent histopathologic study showed more severe CAA but less parenchymal amyloid plaque formation in *APP* duplication than in trisomy 21 patients.<sup>7</sup> Given this diversity in amyloid distribution according to the underlying genetic background, CAA pathogenesis remains to be understood. We here report an *APP* locus triplication, along with relative mRNA expression in the proband's blood.

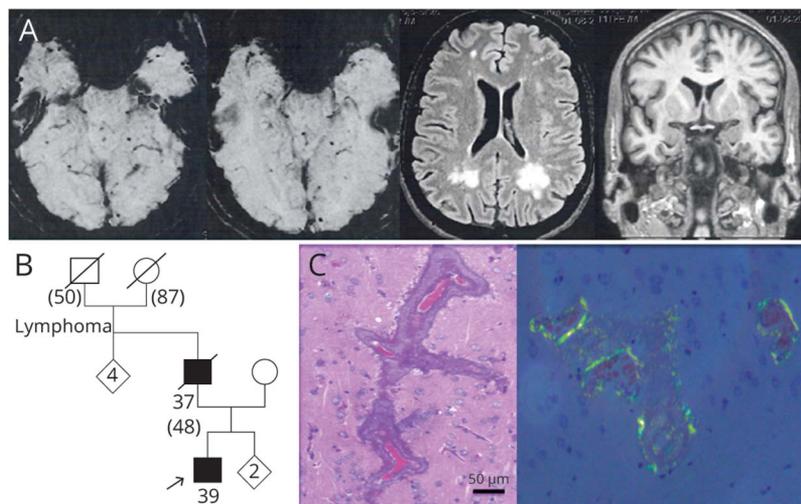
## Case Presentation

A 41-year-old man without medical history was referred to a memory care center for the evaluation of progressive

cognitive decline.<sup>8</sup> From age 39 years, he presented with an aggressive course of episodic memory loss making him unable to maintain his professional activity as well as attention deficit and executive dysfunction. The Mini Mental State Examination (MMSE) scored 18/30 and Frontal Assessment Battery 15/18. There was neither language impairment nor praxis or visuoconstructive dysfunction. The patient did not present any episode suggestive of stroke or seizures. Brain MRI showed multiple lobar microbleeds in the posterior fossa and occipital region and posterior periventricular leukoencephalopathy (Figure 1A) with hippocampal atrophy (bilateral Scheltens scale rating of 2). He underwent lumbar puncture for quantification of CSF AD biomarkers A $\beta$ <sub>42</sub>, tau, and phosphorylated-tau. The A $\beta$ <sub>42</sub> level was decreased (404 ng/L, N > 550), with increased tau (491 ng/L, N < 400) and phospho-tau protein levels (95 ng/L, N < 60). The A $\beta$ <sub>40</sub> level was 8,546 ng/L (4,540 < N < 8,480). Overall, he fulfilled the diagnostic criteria of probable AD with evidence of the AD pathophysiologic process,<sup>8</sup> in association with probable CAA following the modified Boston criteria, except the age criterion.

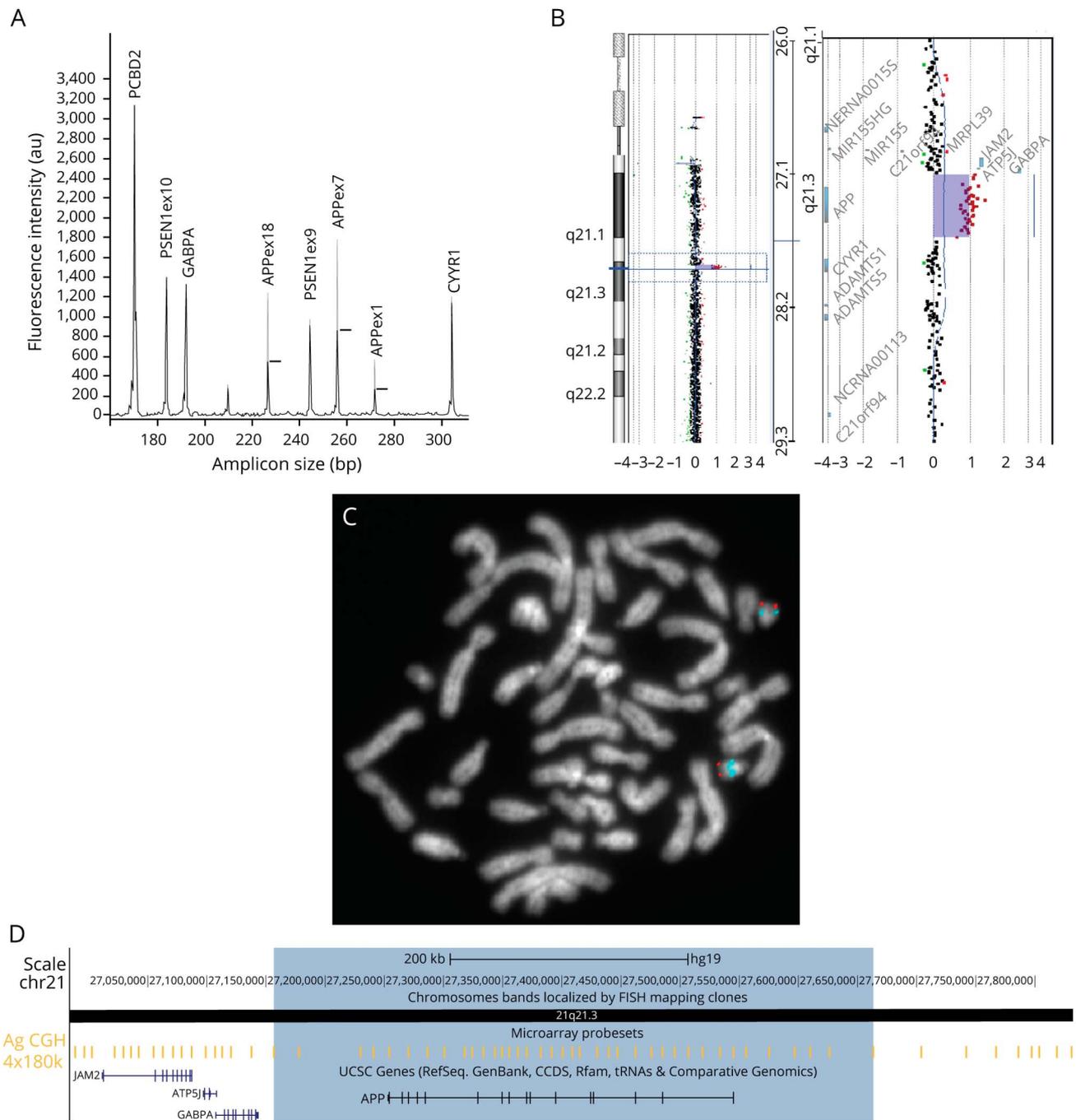
His father had had recurrent migraine with visual aura and presented at age 37 years with transient loss of consciousness (Figure 1B). Focal epilepsy was diagnosed after recurrent episodes of contact loss and electroencephalography showing slow bilateral temporal waves and then treated by carbamazepine. Subsequent cerebral MRI showed hyperintensities in

**Figure 1** Partial Pedigree, Cerebral MRI of the Proband, and Histopathologic Examination of the Cerebral Biopsy Performed in His Father



(A) T2\* weighted sequence showing multiple lobar microbleeds (first and second images); FLAIR-weighted sequence showing posterior leukoaraiosis (third image) and coronal view of T1-weighted sequence showing moderate bilateral hippocampal atrophy (fourth image). (B) Age at death (in parentheses) and age at onset are indicated. The proband is identified by an arrow. (C) Histopathologic examination of the cerebral biopsy of the proband's father. Bouin-fixed paraffin sections of the cerebral biopsy were stained with hematoxylin-eosin (left part) and Congo red (right part). Sections stained with Congo red were examined under crossed polarized light for analyzing vascular amyloid and revealed apple-green birefringence of amyloid material in blood vessel walls.

**Figure 2** Representation of the 21q21.3 Triplication

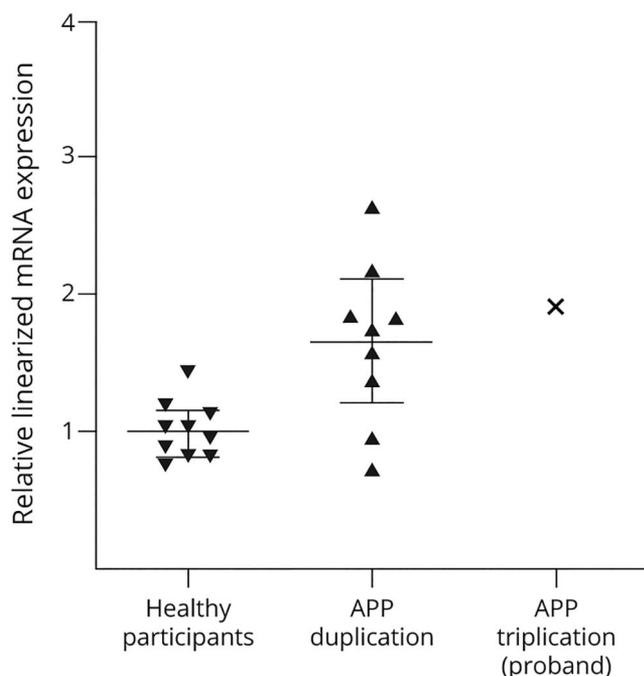


(A) Detection by QMPSF of an *APP* triplication. The electropherogram of the proband (in light gray) was superimposed on that of a normal individual (in black) by adjusting to the same level the peaks obtained from the control amplicon *PCBD2* located on chromosome 5. The vertical axis shows fluorescence in arbitrary units, and the horizontal axis indicates the size of the amplicon in base pairs. Horizontal bars indicate triplication of the amplicons, detected by a 2-fold heightening of the corresponding peaks. This QMPSF also covers 2 genes located at 21q21, *GABPA* and *CYR1* that are not duplicated. (B) Refinement of triplication breakpoints by array CGH. Representation on the Agilent Genomic Workbench 7.0 software of the 21q21.3 triplication (log ratio: 0.97) on chr21: 38,156,233–27,662,338;hg19. (C) FISH analysis of peripheral blood lymphocytes of the proband. Red: control probe located on chromosome 21 long arm subtelomeric region (VJlyRM2029, Vysis; Abbott, Chicago, IL); Blue: *APP* locus specific probe (RP11-410J1; Empire Genomics, Buffalo, NY) located on 21q21.3. (D) Gene content of the triplicated region: Visualization in the UCSC genome browser of the 21q21.3 triplication chr21:27,156,233–27,662,338;hg19 (blue highlight). Yellow bars represent array CGH probes. Yellow bars at both extremes of the blue zone represent the last triplicated probes. The reference assembly used is GRCh37/hg19. Other panels represent, from top to bottom: Agilent 180K probes, cytogenetic band, UCSC genes (only RefSeq sequence). APP = amyloid- $\beta$  precursor protein; FISH = fluorescent in situ hybridization.

centrum semiovale on T2-weighted sequences. CSF was acellular and showed a moderately high protein level (0.61 g/L), but AD biomarkers were not available at this time.

Progressive behavioral disorders and severe cognitive impairment occurred 4 years later and worsened over time with an MMSE of 24/30. Neuropsychological testing showed

**Figure 3** Expression Analysis Using RT-ddPCR



RT-ddPCR with a target amplicon in the *APP* gene and a reference amplicon in the *DLG4* housekeeping gene for healthy controls (N = 10), patients carrying an *APP* duplication (N = 9), and our patient carrying an *APP* triplication (N = 1). Each point represents the average of 3 measures obtained for an individual (except for the proband where the point represents the average of 5 measures). Results are presented through an expression ratio *APP*/*DLG4* linearized with the average expression ratio of controls: For each group, the median relative *APP* mRNA expression is indicated with a wide horizontal line, and 95% confidence intervals are shown with short horizontal lines. *APP* = amyloid- $\beta$  precursor protein; mRNA = messenger RNA; RT-ddPCR = reverse-transcription-digital droplet PCR.

episodic memory loss associated with praxis and visuocognitive moderate dysfunction. He thus fulfilled the diagnostic criteria of probable AD<sup>8</sup> and probable CAA. Tc99m-HMPAO cerebral single photon emission computerized tomography was considered normal. At age 44 years, his condition was extremely severe with repeated loss of consciousness episodes and major upper cerebral dysfunction. Cerebral MRI showed acute bilateral temporal hematomas and posterior leukoencephalopathy. Cerebral angiography did not display any sign of cerebral vasculitis. Cerebral biopsy revealed abundant perivascular amyloid deposits enabling the final diagnosis of probable CAA with supporting pathological evidence (Figure 1C). He died at age 48 years after a second hemorrhagic event with left temporal hematoma. There was no history of dementia or stroke in his family, although a censoring effect was noticed: the paternal grandfather of the proband indeed died at age 50 years from lymphoma (Figure 1B).

## Genetic Assessment

We obtained informed written consent for genetic analyses by the patient and by the father's legal representative. This study was approved by the Institutional Review Board of Rouen University Hospital (CERDE #2019-55 notification).

Quantitative multiplex PCR of short fluorescent fragment (QMPSF) analyses performed from DNA isolated from fresh whole blood revealed 4 copies of the *APP* gene in the proband (Figure 2A). His *APOE* genotype was 33, and Sanger sequencing did not detect any point mutation in exons 16–17 of *APP*. The 68-year-old unaffected mother carried 2 copies of *APP*, suggesting a 3 + 1 genotype in the proband, but no DNA sample was available from his father. Fluorescent in situ hybridization using *APP* locus specific probes (RP11-410J1; Empire Genomics, Williamsville, NY) on cultured lymphocytes metaphase cells showed an asymmetric positive hybridization signal on chromosome 21 long arm without other signal hybridization anywhere else (Figure 2C), further suggesting a 3 + 1 genotype and hence autosomal dominant transmission of a triplication.

We further mapped the triplication using array comparative genomic hybridization (aCGH, Agilent SurePrint 4 × 180k; Agilent Technologies, Santa Clara, CA). The 506-kb 21q21.3 triplication (chr21:27,156,233-27,662,338;hg19) was restricted to the whole *APP* gene without any flanking gene coding sequence (Figure 2, B and D).

Finally, mRNA *APP* levels were assessed using reverse-transcription–digital droplet PCR in the proband whole blood comparatively to 10 normal controls (including the proband's mother) and 9 patients carrying *APP* duplications (see eMethods, links.lww.com/NXG/A465). The patient showed a 2-fold increase of relative *APP* mRNA levels compared with controls (Figure 3 and eFigure 1, links.lww.com/NXG/A470). Patients with *APP* duplication showed a median of 1.8 fold increase compared with controls, but no comparison could be directly made with our proband, considering this single *APP* triplication case.

## Discussion

To our knowledge, this is the first report of an *APP* locus triplication, causing a two-fold upregulation of *APP* mRNA levels, in a family presenting with autosomal dominant EOAD with severe CAA. Although duplications of a given gene are now a classical cause of several autosomal dominant disorders, there are few examples of mendelian diseases caused by a gene triplication. In the field of neurodegenerative diseases, *SNCA* triplications on chromosome 4 have been reported in patients with Parkinson or Lewy body disease along with duplications in other patients.<sup>9</sup> As for the *APP* gene, alpha-synuclein-encoding *SNCA* increased gene copies encompassed at least the *SNCA* gene, with or without surrounding genes (1 to 50), and displayed high diversity in clinical phenotype.<sup>10</sup> Similarly, since its first description, some diversity of phenotypes associated with *APP* duplications has been described, mostly related to the predominance of AD or CAA-related symptoms at presentation.<sup>6</sup> In this report, triplication was associated with diverse presentation, including severe cognitive disorder in the proband and recurrent ICH and seizures in his father.

The higher copy number seemed to be associated with earlier symptomatic phase in our report (37 and 39 years of age at onset) compared with *APP* duplication carriers showing ages at onset ranging from 39 to 65 years.<sup>1,4-6</sup> However, we can expect some degree of diversity in ages of onset in other *APP* triplication families.

In a recent French series of EOAD, *APP* duplication carriers were more likely to present with seizures,<sup>11</sup> possibly explained by A $\beta$  overproduction related to increased *APP* expression. Early seizures may be a shared clinical feature with *APP* triplication as observed in the father of the proband.

Different mechanisms can be involved in autosomal dominant CAA and AD pathogenesis. In contrast with *APP* point mutations, which can result in increased beta cleavage of *APP*, change in A $\beta$ 42/38 ratio, or in A $\beta$  aggregation propensity,<sup>12</sup> *APP* duplications lead to *APP* overproduction, with severe A $\beta$  deposits in the brain parenchyma and within vessels walls.<sup>1,3</sup> Here, cerebral biopsy of the proband's father confirmed severe amyloid perivascular deposits consecutive to *APP* overproduction. Indeed, we found a 2-fold upregulation of *APP* mRNA levels in blood. Unfortunately, no comparison could be made with *APP* duplication carriers given the availability of RNA in the proband only so that we cannot be sure that triplications result in significantly increased mRNA levels than in duplication.

Here, we showed by aCGH that the triplication encompassed the *APP* gene only. To our knowledge, there is a single case report of an *APP* duplication encompassing the *APP* gene solely, highlighting that increased *APP* expression is sufficient to cause EOAD and CAA.<sup>2</sup> However, the resolution of the techniques did not allow us to assess whether the breakpoints were the same in our case and in this 290–750 kb duplication.<sup>2</sup> The mechanisms underlying genomic instability of the *APP* region remain elusive, and further reports are needed to refine shared or novel breakpoints.

Overall, our report provides further evidence that increased *APP* expression is sufficient to lead to A $\beta$  aggregation and subsequent EOAD and CAA. Although ages at clinical onset were among the earliest ones in our *APP* triplication carriers compared with duplication carriers, further cases would be required to conclude.

## Study Funding

No targeted funding reported.

## Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/NG](http://Neurology.org/NG) for full disclosures.

## Publication History

Received by *Neurology: Genetics* April 1, 2021. Accepted in final form June 8, 2021.

## Appendix Authors

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Continued

## Appendix (continued)

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<b>Gael Nicolas, MD, PhD</b>	Department of Genetics and CNR-MAJ, Normandie University, UNIROUEN, Inserm U1245 and CHU Rouen, F-76000 Rouen, France	Study concept, interpretation of data, and drafting and manuscript revision

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*Neurol Genet* 2021;7;

DOI 10.1212/NXG.0000000000000609

**This information is current as of September 8, 2021**

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