

# A novel *SORL1* mutation in a pedigree affected by early-onset Alzheimer's disease

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## Abstract

Familial cases of Alzheimer's disease (AD) with autosomal dominant transmission and early onset have a prevalence around 1%. Since only a small fraction of them has a monogenic inheritance due to *APP*, *PSEN1*, and *PSEN2* genes, genetic studies are ongoing to unravel the missing heritability. By sequencing panels including multiple dementia-related genes, we identified a novel likely pathogenic mutation in *SORL1* in a pedigree including five members affected by AD. This loss of function mutation may lead to a reduction of *SORL1* receptor, worsening amyloidogenic burden. As the contribution of *SORL1* mutations to heritability of AD is presently not well established, we think that it is very important to signal new familial (likely) pathogenic *SORL1* mutations in order to define the actual genetic involvement of *SORL1* in AD pathogenesis.

## Keywords

Alzheimer's disease, FDG-PET, early-onset, mutation, next generation sequencing, *SORL1*

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## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and a major cause of dementia in the elderly population. AD is clinically characterized by progressive memory decline and impaired executive functions, including difficulties in daily activity; behavioral and languages disturbances can also be present. Primary pathological hallmarks of AD include amyloid- $\beta$  (A $\beta$ ) plaques, neurofibrillary tangles, and neuronal loss.<sup>1</sup> While AD is mostly sporadic in its common late-onset occurrence, there are also rare early-onset (<65 years) autosomal dominant forms that have a prevalence <1%, with only about 5–10% of them being linked to three major genes, namely *APP*, *PSEN1*, and *PSEN2*.<sup>2</sup> Several pedigrees are known showing an apparently autosomal dominant pattern of inheritance, but without mutations in these genes, thus raising the need to unravel additional genetic causes of a missing heritability. Furthermore, neurodegenerative diseases leading to dementia can show wide phenotypic variability, associated with several genetic defects.<sup>3</sup> The recognition of this clinical and genetic heterogeneity suggests employing extensive genetic testing, such as next generation sequencing (NGS)

analysis of multiple gene panels, especially in familial cases and/or in presence of presenile disease onset, to disclose genetic determinants of disease.

Here we present the case of a woman affected by AD with a remarkable family history, whose analysis of *APP*,

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*PSEN1*, and *PSEN2* gave negative results. The patient underwent a complete diagnostic protocol including a wide genetic screening related to several dementia genes. We disclosed a variant (R67GfsTer32) in Sortilin-related receptor 1 (*SORL1*) gene, whose functions include controlling trafficking and processing of APP and lysosomal degradation of Aβ peptides.<sup>4</sup>

Case report

This study was performed in line with the principles of the Declaration of Helsinki. Informed consent was obtained from all individuals included in the study. Ethics approval was waived by the local Ethics Committee as all the performed procedures were part of the routine care.

Proband

A 59-year-old woman came to our Institute with a clinical presentation of mild dementia. She reported cognitive alterations characterized by memory loss over the preceding two years, with difficulty remembering appointments or what to cook. She often needed to write things to do, and in the gym, she struggled to remember the exercises to perform.

Routine laboratory testing ruled out reversible causes of cognitive impairment, including hypothyroidism, B12 and folate deficiency, syphilis, and HIV. Neurologic examination was unremarkable. Cerebrospinal fluid (CSF) AD biomarkers (Lumipulse system, Fujirebio) showed pathological level of Aβ<sub>42</sub>, with reduction of Aβ<sub>42</sub>/Aβ<sub>40</sub> ratio, while phosphorylated tau and total tau were normal (Table 1). A brain magnetic resonance imaging (MRI) was normal, without signs of cortical atrophy. An <sup>18</sup>F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) scan of the brain showed mildly reduced metabolism in the lateral parietal cortex, precuneus, and temporal lobe, asymmetric due to greater severity on the right, with a metabolic pattern indicative of early AD (Figure 1). Although in AD the hypometabolism is usually symmetrical, in the initial stages of the disease the finding of asymmetric hypometabolism is common. A comprehensive neuropsychological assessment was performed, and the results showed multi-domain amnesic mild cognitive impairment (Table 1). A diagnosis of prodromal AD was advanced.

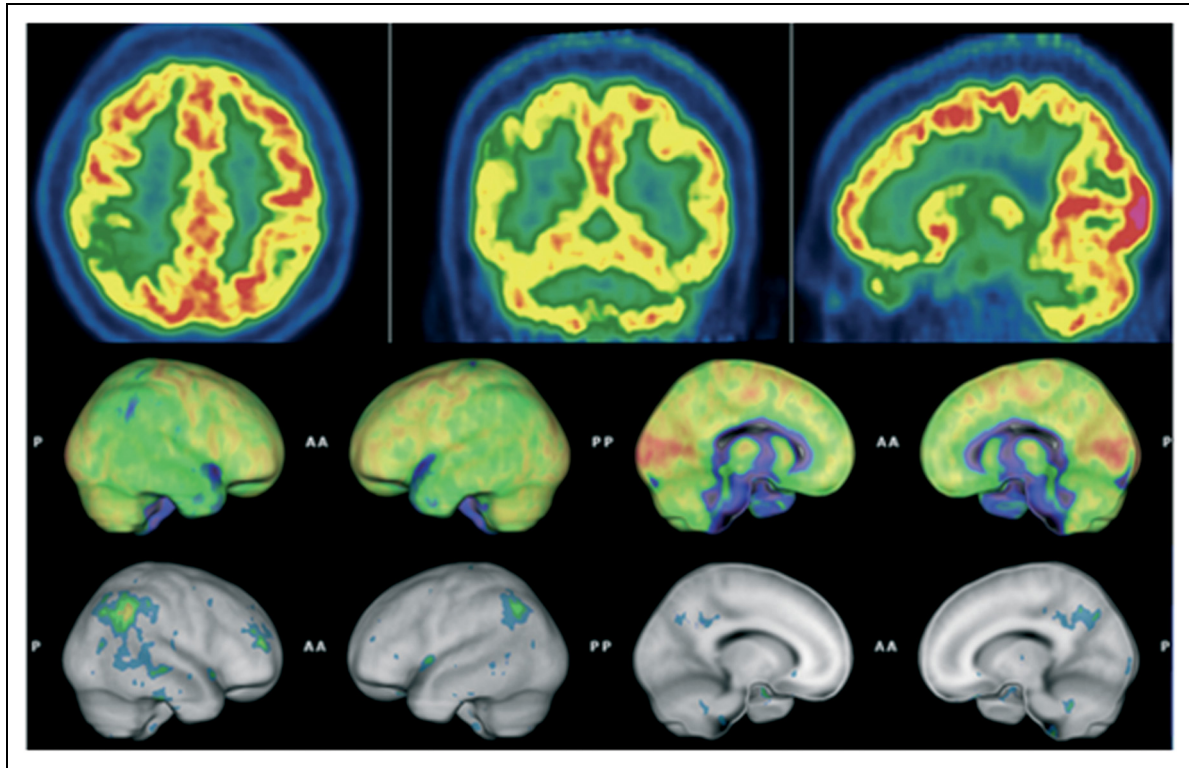
Proband's sister

A sister presented at age 63 with behavioral disorders such as irritability; after two years, memory deficits also appeared (she left the iron and fire on). At age 68, memory deficits were more significant, a cerebral single

Table 1. Demographic, clinical, imaging, and CSF data of the patients.

|         | Age at onset | Clinical signs at onset | Clinical signs at follow-up         | Cognitive profile                                                                                                                                                                                       | Imaging                                                                                                                                                                                    | Aβ <sub>42</sub>      | Aβ <sub>42</sub> /Aβ <sub>40</sub> ratio | p-tau 181                  | Total tau               |
|---------|--------------|-------------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|----------------------------|-------------------------|
| Proband | 57           | Memory loss             | Memory loss                         | multi-domain amnesic mild cognitive impairment with visuospatial and episodic memory disturbances and mild constructional apraxia                                                                       | <b>MRI:</b> normal<br><b>FDG-PET:</b> mildly reduced metabolism in lateral parietal cortex, precuneus, and right temporal lobe                                                             | 304*<br>(n.v., > 640) | 0.040<br>(n.v., 0.068–0.115)             | 49.3*<br>(n.v., 21.5–56.5) | 287*<br>(n.v., 146–404) |
| Sister  | 63           | Behavioral disorders    | Behavioral disorders<br>Memory loss | space-time disorientation, memory disturbances, difficulties with executive functioning, apraxia and aphasia. Behavioral disturbances: emotional lability, delusions, fatuity, irritability, wandering. | <b>MRI:</b> diffuse and severe cortical atrophy<br><b>FDG-PET:</b> severely reduced metabolism in parietal, temporal, and frontal regions<br><b>SPECT:</b> frontal bilateral hypoperfusion | na                    | na                                       | na                         | na                      |

CSF: cerebrospinal fluid; n.v.: normal values; na: not available. \*The units are pg/ml.



**Figure 1.** Top row: axial, coronal and sagittal FDG-PET images of proband, showing mild reduction in cerebral metabolism in the lateral and mesial parietal cortex and in the temporal lobe, more evident on the right. Middle row: Voxel-based analysis of FDG-PET (SSP): the images show the distribution of metabolism projected onto a reference brain atlas. Bottom row show the regions where the z-score is below 2.5, compared to a population of subjects of the same age. The SSP analysis detects areas of significant reduction in cerebral metabolism in the parietal lobe and in the precuneus, bilaterally, and in the temporal lobe cortex on the right.

photon emission computed tomography (SPECT) showed frontal bilateral hypoperfusion and an MRI showed diffuse and severe cortical atrophy; a FDG-PET (Figure 2) showed widespread severe reduction in cerebral glucose metabolism, particularly severe in the parietal, temporal, and frontal regions, consistent with a diagnosis of AD in the late stage. Primary sensory and motor cortex regions were typically spared. No CSF biomarkers were available. A cognitive evaluation showed a severe dementia associated with behavioral disturbances at onset, followed by memory loss (Table 1).

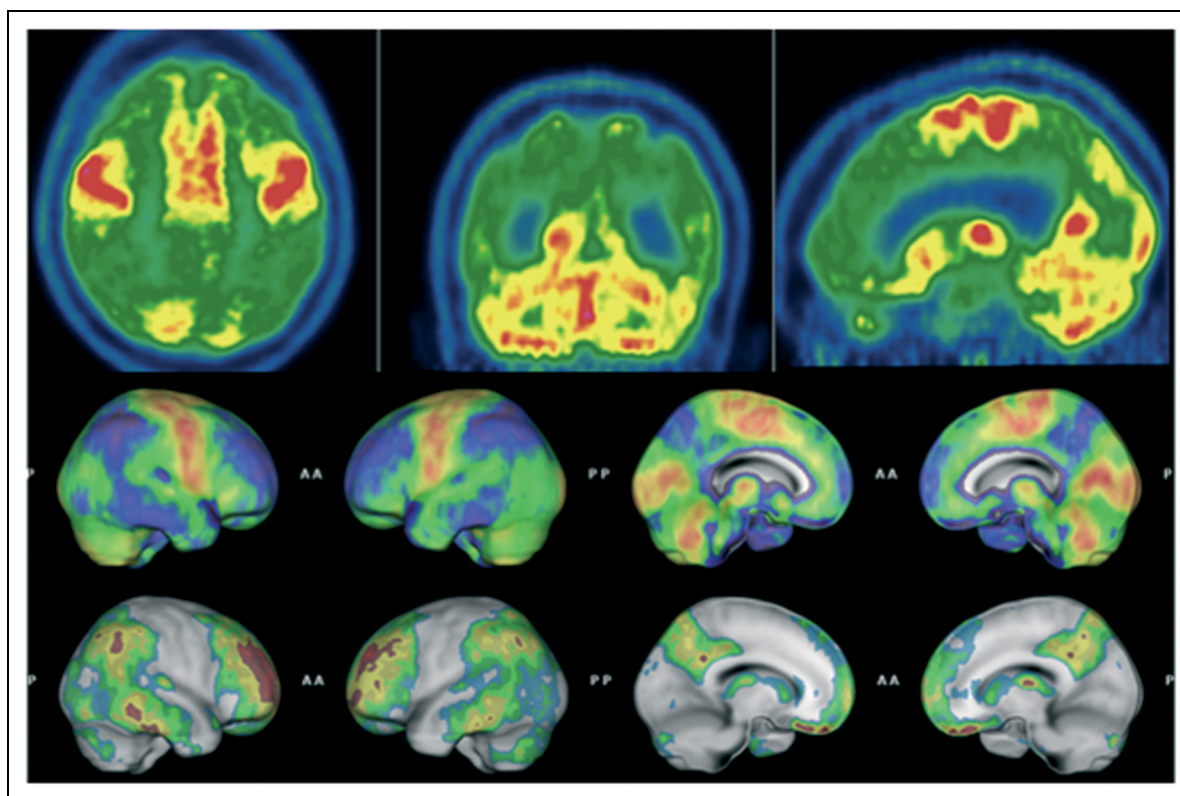
The mother (age of onset 45, death at 52) and two maternal uncles received the diagnosis of early-onset AD. Maternal grandfather died young without specific information about the causes of death.

Table 1 includes demographic, clinical, imaging, and CSF data of the patients.

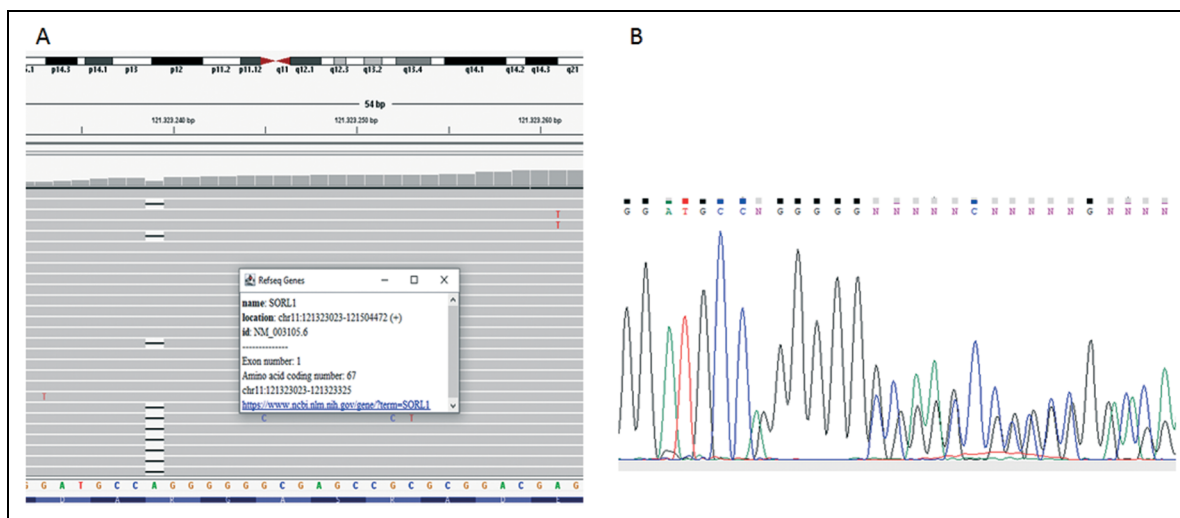
Extensive genetic study was carried out by NGS on the proband. A targeted custom panel of causal and rare/risk genes known to be associated with dementia was analyzed, including: *APP*, *PSEN1*, *PSEN2*, *PRNP*, *GRN*, *MAPT*, *CHMP2B*, *FUS*, *TARDBP*, *VCP*, *TREM2*, *ABCA1*, *ABCA7*, *ADAM10*, *AKAP9*, *APOE*, *BCL7C*, *BIN1*, *CALHMI*,

*CCL2*, *CCNF*, *CD2AP*, *CD33*, *CHCHD10*, *CLU*, *CSF1R*, *CST3*, *CTSF*, *CXCR4*, *DCTN1*, *EIF4G1*, *EPHA1*, *FLNC*, *GABRB3*, *GBA*, *GIGYF2*, *GSN*, *hnRNPA1*, *hnRNPA2B1*, *ITM2B*, *LRRK2*, *NCSTN*, *NOS3*, *NOTCH3*, *NPC1*, *NPC2*, *OPTN*, *PFN1*, *PICALM*, *PINK1*, *PLD3*, *PRKAR1B*, *PRKN*, *SCARB2*, *SERPINI1*, *SIGMAR1*, *SNCA*, *SNCB*, *SOD1*, *SORL1*, *SORT1*, *SQSTM1*, *STH*, *STX1B*, *TBK1*, *TIA1*, *TMEM106B*, *TSC1*, *TTR*, *TUBA4A*, *TYROBP*, *UBQLN2*, *UNC5C*. The study was performed with the Nextera Flex for enrichment kit (Illumina) coupled with gene-specific probes (Integrated DNA Technologies) and MiSeq instrument (Illumina). MiSeq Reporter software (Illumina) was used for alignment (reference human genome UCSC hg19) and DNA variants were analyzed with Variant Studio software (Illumina), in addition to an in-home made bioinformatics pipeline.

While the major AD genes (*APP*, *PSEN1*, and *PSEN2*) were negative, the analysis disclosed the heterozygous variant NM\_003105.5:c.199delA, resulting to R67GfsTer32 at protein level, in *SORL1* (Figure 3). This variant, confirmed using standard Sanger sequencing, has not been previously described in any control or disease database and it is classified as “likely pathogenic” according



**Figure 2.** Axial, coronal and sagittal FDG-PET (top row), SSP analysis (middle row) and z-score maps (bottom row) of proband's sister. Images show severe reduction in cerebral metabolism in the parietal, temporal and frontal lobes. SSP analysis confirms the high significance of the hypometabolism in the associative cortex in parieto-temporal regions and in the frontal lobe, while primary motor and visual cortex are normal.



**Figure 3.** (A, B) Genetic analysis of proband. (A) NGS sequencing results displayed on the genome browser visualization tool Integrative Genome Viewer (IGV). The A deletion in the AGG codon at position 67 is shown. (B) Sanger sequencing confirming the deletion with the resulting frame-shift.

to American College of Medical Genetics criteria.<sup>5</sup> In particular, the variant met the “Effect on protein” PVS1 (pathogenic very strong) and the “Population data” PM2

(pathogenic moderate) criteria, according to both Varsome (<https://varsome.com/>) and Franklin by Genoox (<https://franklin.genoox.com/clinical-db/home> analysis) analyses.

The proband's sister also underwent the complete NGS analysis and the same *SORL1* variant was detected, strongly supporting its pathogenic nature. Genotyping of *APOE* showed  $\epsilon 3/\epsilon 4$  alleles in both patients.

## Discussion

*SORL1*, also known as *LR11* or *SORLA*, encodes a large, multi-domain, membrane-bound receptor, widely expressed in the brain. At the plasma membrane, it can follow a signaling or a trafficking pathway.<sup>6</sup> As for the trafficking pathway, it is involved in sorting of different proteins and, in particular, of amyloid- $\beta$  protein precursor (A $\beta$ PP), guiding intracellular trafficking and processing of this protein. A $\beta$ PP undergoes a series of trafficking steps within cells. Nascent A $\beta$ PP protein is generated in ER, processed in the Golgi and transported through secretory vesicles to the cell surface. At the cell surface, most A $\beta$ PP molecules are cleaved in the non-amyloidogenic pathway, while some A $\beta$ PP is internalized by clathrin-mediated endocytosis and directed to endosomes. In late endosomes, sequential cleavage by the  $\beta$ - and the  $\gamma$ -secretases results in the production of the A $\beta$  peptide which can then be secreted in the extracellular compartment or be directed to lysosomes. *SORL1* can bind both A $\beta$ PP and A $\beta$  and act as a repressor of A $\beta$  secretion, both by redirecting A $\beta$ PP to the plasma membrane or by targeting A $\beta$  peptides to lysosomes for degradation.<sup>4</sup>

Thus, *SORL1* can contribute to the reduction of the amyloidogenic burden. Therefore, it is not surprising that reduced expression or altered *SORL1* activity, induced by genetic variants in the *SORL1* gene, might lead to an increase in A $\beta$  that, in turn, contributes to the pathogenesis of AD.<sup>7</sup> In fact, the heterozygous variant NM\_003105.5:c.199delA is located in exon 1 of *SORL1* at codon 67 and causes a protein frame-shift leading to a STOP codon after 32 amino acids. This 98 amino acid abnormal peptide is very likely unstable and subjected to degradation, leading to *SORL1* protein reduction, which may be deleterious for its function, including A $\beta$ PP and A $\beta$  metabolism.

Endo-lysosomal pathways sustain essential physiological functions in the cells, and several genes coding for proteins involved in these pathways are associated with neurodegenerative diseases, as failure of proper protein trafficking and degradation could underlie neuronal dysfunction.<sup>8</sup> As for *SORL1*, although primarily associated with AD, rare variants have been found in frontotemporal dementia and Lewy body disease cases,<sup>9,10</sup> qualifying *SORL1* as a cross-disease gene and underlying the common pathological pathways which are behind these brain diseases.<sup>10</sup>

*SORL1* appears to have a strong association with the occurrence of both late onset, sporadic form of AD and less frequent, early onset, familial form of AD. The first evidence came from case-control studies based on common

SNP variants present in 6 candidate genes, among which there was *SORL1*, for which two associated haplotypes were identified.<sup>11</sup> Further genome-wide association studies showed that *SORL1* was one of the 20 loci associated with AD risk with genome-wide significance (p value threshold:  $<5 \times 10^{-8}$ ).<sup>12</sup>

Due to the development of NGS, whole exome sequencing allowed the detection of rare (minor allele frequency  $\leq 1\%$ ) coding variants, evaluated both as single variants or collapsed in the gene-based analysis.<sup>4,13</sup> In particular, for *SORL1*, truncating variants (creating a Stop codon) and missense variants defined as pathogenic according to multiple *in silico* tools, were detected in several studies, even reaching the so-called exome-wide significance (p value threshold:  $<2.5 \times 10^{-6}$ ), in late-onset AD (LOAD) as well in early-onset AD (EOAD), with odd ratios higher than for the common variants previously studied and increasing from LOAD to apparently sporadic EOAD to EOAD with positive family histories showing autosomal dominant patterns.<sup>4</sup>

Since a number of families with autosomal dominant inheritance of EOAD are not accounted for by *APP*, *PSEN1*, or *PSEN2* mutations, a search for additional genetic causes is required. In a *SORL1*-centered study, in 7 out of 29 such families, *SORL1* putative pathological variants were identified, although a segregation analysis could not be performed, except in one case;<sup>14</sup> similarly, in a more recent study, 6 AD families carrying a *SORL1* variant have been reported, autosomal dominant inheritance being present in 3 of them.<sup>15</sup> Anyway, some pedigrees have been described where rare *SORL1* variants segregated with EOAD<sup>16,17</sup> or LOAD.<sup>7</sup>

In the same line, in our family, five subjects in two generations were reported as affected by AD, with apparent autosomal dominant inheritance and positive segregation.

Thus, based on the wide amount of these data, the question has arisen whether *SORL1* may be considered an AD monogenic causative gene alongside with *APP*, *PSEN1*, and *PSEN2*, further supporting the central role of amyloidogenic processing in the etiology of this disorder. Presently, some critical elements must be taken into account: (i) the co-occurrence of additional variants in other risk genes such as *ABCA7*,<sup>18</sup> or modifier genes such as *APOE*<sup>17</sup>; (ii) the existence of several families in which the segregation is imperfect, with the presence of elderly non affected subjects carrying the variant or affected subjects without the variant.

There are some limits in this study: (i) The presence in our patients of one  $\epsilon 4$  allele in *APOE*, a well-known risk factor for AD development, may, on one hand, be considered to reinforce the effect of the R67GfsTer32 *SORL1* variant on the severity of disease but, on the other hand, it may be a confounding factor as for the causative nature of the variant. This was also pointed out in previously published reports.<sup>17</sup> (ii) In addition, functional studies are



lacking, while they would be of utmost interest to define the influence of this *SORL1* variant on A $\beta$ PP metabolism.

To settle the question whether *SORL1* can be considered an AD causative gene, more pedigree-based segregation studies are needed, together with studies on age-related penetrance provided with an adequately high number of patients. In addition, the effect of modifier genes must be deeply investigated. Accordingly, we think that it is very important to signal familial cases due to (likely) pathogenic *SORL1* variants, such as our pedigree, to add to future analyses in order to define the real genetic contribution of *SORL1* to AD pathogenesis.

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## Statements and declarations

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### Data availability

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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