

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/radcr](http://www.elsevier.com/locate/radcr)

## Case Report

# Early-onset Alzheimer's disease may be associated with sortilin-related receptor 1 gene mutation: A family report and review <sup>☆</sup>

Liming Cao, MD<sup>a,b,\*</sup>, Feiqi Zhu, MD<sup>a</sup>, Guozhen Qiu, MD<sup>a</sup><sup>a</sup> Department of Neurology, The Third Affiliated Hospital of Shenzhen University, Shenzhen, China<sup>b</sup> Department of Neurology, Shenzhen University First Affiliated Hospital, Shenzhen, China

## ARTICLE INFO

## Article history:

Received 27 September 2020

Revised 12 October 2020

Accepted 17 October 2020

## Keywords:

Early-onset Alzheimer's disease

SORL1 gene mutation

Magnetic resonance imaging

Hippocampal atrophy

Cognitive impairment

## ABSTRACT

**Background:** Early-onset Alzheimer's disease is a rare condition that differs from the usual memory-disordered presentation of typical Alzheimer's disease. Early-onset Alzheimer's disease is believed to have a genetic basis, and sporadic Alzheimer's disease has been associated with sortilin-related receptor 1 polymorphism.

**Case presentation:** This report describes and discusses the family report of a 59-year-old patient with early-onset Alzheimer's disease that may have been associated with a sortilin-related receptor 1 gene mutation. The patient was hospitalized in August 2008 for gradually progressive amnesia. Brain magnetic resonance imaging showed that the patient presented with whole-brain atrophy (especially in the bilateral medial temporal lobe and hippocampus). He had an initial Mini-Mental State Examination score of 15 (time orientation: 4/5; place orientation: 4/5; language immediate memory: 2/3; attention and calculation: 1/5; delayed memory: 0/3; naming: 1/2; language retelling, understanding, and expression: 3/6; visuospatial ability: 0/1). Whole-exome sequencing showed a sortilin-related receptor 1 gene mutation, c.3575G>A (chr11:121448104), which was detected in the patient and his children.

**Discussion:** Patients with early-onset Alzheimer's disease present with obvious deficits in language, visuospatial abilities, praxis, or other nonmemory cognitive functions. In this case, the speech, memory, and visuospatial impairment of the patient may be associated with the sortilin-related receptor 1 gene mutation. Atrophy of the bilateral medial temporal lobe/hippocampus on magnetic resonance imaging may be an important marker of early-onset Alzheimer's disease. A sortilin-related receptor 1 gene mutation, c.3575G>A (chr11:121448104), may increase the risk of Alzheimer's disease.

© 2020 The Authors. Published by Elsevier Inc. on behalf of University of Washington.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)<sup>☆</sup> Conflicts of interest and source of funding: None.

\* Corresponding author.

E-mail address: [caolm-2007@163.com](mailto:caolm-2007@163.com) (L. Cao).<https://doi.org/10.1016/j.radcr.2020.10.030>1930-0433/© 2020 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

---

## Introduction

Early-onset Alzheimer's disease (EOAD) is a rare condition that presents with the same phenotype seen in Alzheimer's disease (AD), but with an earlier onset, at an age younger than 65 years. EOAD comprises approximately 5% of AD cases and is associated with a delayed diagnosis, aggressive disease course, and age-related psychosocial needs [1]. Indeed, EOAD differs significantly from the more common late-onset AD (LOAD). Patients with EOAD and LOAD have been found to show distinct patterns of memory impairment [2]. Many patients with EOAD exhibit phenotypic variants that differ from the usual memory-disordered presentation of typical AD. EOAD is believed to have a genetic basis, and sporadic AD has been associated with sortilin-related receptor 1 (SORL1) polymorphism; the SORL1 gene is closely related to cognitive function, such as memory, executive function, language, and abstract reasoning. However, despite the efforts to identify the contribution of causative genes to EOAD, its atypical disease presentation and signs result in its diagnosis and treatment, remaining a challenge for clinicians [3]. Early diagnosis of EOAD is difficult, as it shows nonspecific symptoms and is often misdiagnosed as frontotemporal dementia or other diseases. In this article, we describe and discuss a family report of a patient with EOAD related to SORL1 gene mutation, which can help in the effective diagnosis of conditions such as EOAD.

---

## Case presentation

A 59-year-old male patient was hospitalized in August 2008 for amnesia that had slowly become worse over the past 3 years. The patient's memory was very poor, to the point that he would forget what he had eaten immediately after eating and would easily become lost. He was unable to pay for purchases with cash by himself (which had never been an issue before) and was dismissed from his job because of the memory impairment. The patient exhibited no limb hemiplegia, no eating disorder, no irregular stool function, and no significant weight loss in the past 3 months. He had a poor appetite and disrupted sleep. Two years prior, he had undergone extracorporeal shock wave lithotripsy and left percutaneous nephrostomy of the left kidney. Benign prostatic hyperplasia and hepatic cyst were present for longer than 1 month before admission. The patient had no history of hypertension, coronary heart disease, diabetes, major trauma, infectious disease, or allergy. He had no family history of dementia.

At admission, a physical examination showed that the patient was lucid and had poor memory and computational ability, slow speech, no obvious abnormality of cranial nerve function, normal muscle strength and muscle tension, normal sensory function of the limbs, no ataxia, and no pyramidal tract signs. An auxiliary examination was also performed. The urine analysis revealed the following: nitrite: present, protein: present, ketone body: present, red blood cells:

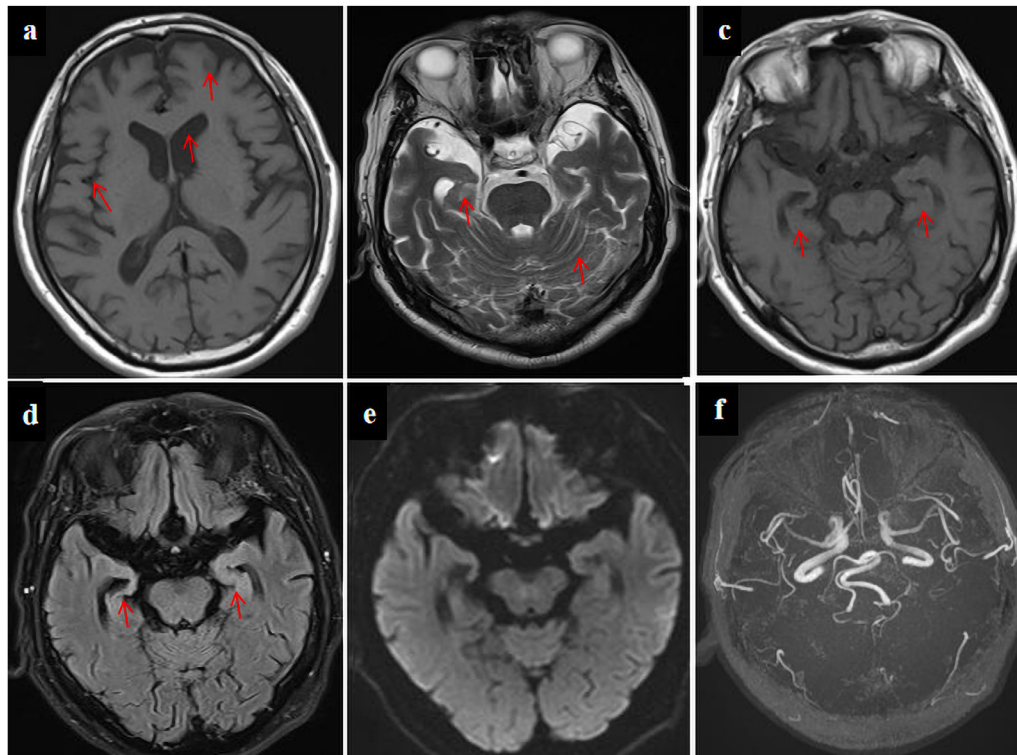
226/ $\mu$ L, and white blood cells: 132/ $\mu$ L. The routine stool examination was normal. The result of the stool occult blood test was positive. The blood lipid test revealed the following: triglyceride: 2.22 mmol/L; low-density lipoprotein: 3.27 mmol/L; high-density lipoprotein: 0.86 mmol/L; apolipoprotein A: 0.98 g/L; apolipoprotein B: 1.13 g/L; and total cholesterol: 5.68  $\uparrow$ mmol/L. The renal function test revealed a uric acid concentration of 430  $\uparrow$  $\mu$ mol/L. The patient was negative for human immunodeficiency virus and syphilis antibodies, glycosylated hemoglobin, and myocardial enzymes. The presence of the AD-associated neurofilament protein in his urine was negative (0.64 ng/mL). Chest and abdominal radiographs revealed aortic tortuosity, no obvious abnormal changes in the pulmonary field or diaphragm on both sides, and a double J stent in the left ureter. Brain magnetic resonance imaging (MRI), functional diffusion imaging, and MR angiography revealed whole-brain atrophy (especially in the bilateral medial temporal lobe and hippocampus; see Fig. 1) and mild stenosis of the clinoid segment of the left internal carotid artery and the M1 segment of the right middle cerebral artery. Color Doppler ultrasonography of the abdomen revealed no abnormal findings. He had a Mini-Mental State Examination (MMSE) score of 15: time orientation: 4/5; place orientation: 4/5; language immediate memory: 2/3; attention and calculation: 1/5; delayed memory: 0/3; naming: 1/2; language retelling, understanding, and expression: 3/6; and visuospatial ability: 0/1. Whole-exome sequencing was performed by Running Gene Inc. (Beijing Jinjun Gene Technology Co. Ltd., Beijing, PR China) according to the manufacturer's protocol in the proband. Sanger sequencing was then performed for validation in the patient's son and daughter. An SORL1 gene mutation, c.3575G>A (chr11:121448104), was detected in the patient and his children (see Fig. 2). Genetic testing revealed he was carrying the ApoE3 allele.

The patient was diagnosed with EOAD potentially associated with SORL1 gene mutations. The patient was treated for 1 week with a view to improving cerebral circulation (intravenous Ginaton 35 mg/day; Dr Willmar Schwabe Pharmaceutical Co., Karlsruhe, Germany), to provide neurotrophic treatment (intravenous Citicoline 0.3 g/day; Bainian Hank Pharmaceutical Co.), and improve memory (Donepezil Hydrochloride tablets 5 mg/day). At the end of the 1 week of treatment, the patient's cognitive status seemed to have slightly improved (MMSE score: 16). The patient and his children provided informed consent for the publication of this case report.

---

## Discussion

Although most research on AD has concentrated on LOAD, EOAD has been the focus of much recent interest. We found that in this case, not only was the onset age earlier and the bilateral medial temporal lobe atrophy obvious but also the manifestations involved executive speech, memory, and visuospatial impairment (differing from the manifestations seen in LOAD). This etiology may be related to the SORL1 gene mutation (c.3575G>A (chr11:121448104)), which has been rarely reported before.



**Fig. 1** – Axial T1-weighted magnetic resonance imaging (MRI) shows cerebral cortex atrophy, enlarged sulci, and a dilated lateral ventricle (a, arrows); Axial T2-weighted MRI shows bilateral hippocampal atrophy and the enlarged sulci of the cerebellar hemisphere (b, arrows); T1-weighted MRI (c, arrows) and fluid attenuated inversion recovery sequence (d, arrows) show bilateral hippocampal atrophy; Diffusion-weighted imaging shows no lesion of restricted diffusion (e); Axial magnetic resonance angiography shows no obvious cerebral artery abnormalities (f).

#### *Differences in cognitive impairment between EOAD and LOAD*

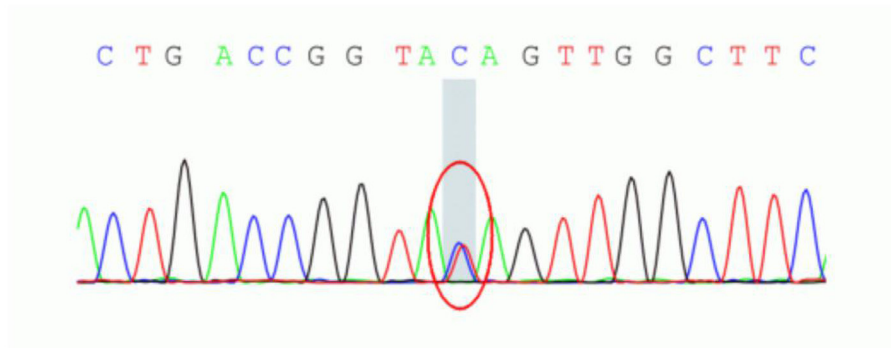
While current research primarily focuses on LOAD rather than EOAD, there are significant differences between the two [1]. Mutations of the *SORL1* gene are closely related to the impairment of cognitive functions such as memory, executive function, language, and abstract reasoning [4]. Compared with LOAD, EOAD has a larger genetic predisposition, a more aggressive course, a longer delay in diagnosis, a higher prevalence of traumatic brain injury, less memory impairment, greater involvement of other cognitive domains on presentation, and greater psychosocial difficulties [5]. Approximately 22%-64% of patients with EOAD have a predominant non-amnesic syndrome presenting with deficits in language, visuospatial abilities, praxis, or other nonmemory cognitive functions [6]. EOAD and LOAD were similarly affected on the measures of episodic, short-term, and working memory, but semantic memory was significantly more impaired in patients with LOAD than in those with EOAD [2]. That study also found that patients with EOAD exhibited significantly poorer performance than did those with LOAD in other cognitive domains, including executive functions and visuospatial abilities [2]. In another study, patients with EOAD performed worse in attention, imitation, praxis, and verbal learning tests than those with LOAD [7]. The memory, speech, and executive function of the patient whose case we presented in this paper were

affected, which is consistent with the description in the aforementioned studies [2,4,6,7], and confirms that EOAD and LOAD groups show distinct patterns of cognitive impairment.

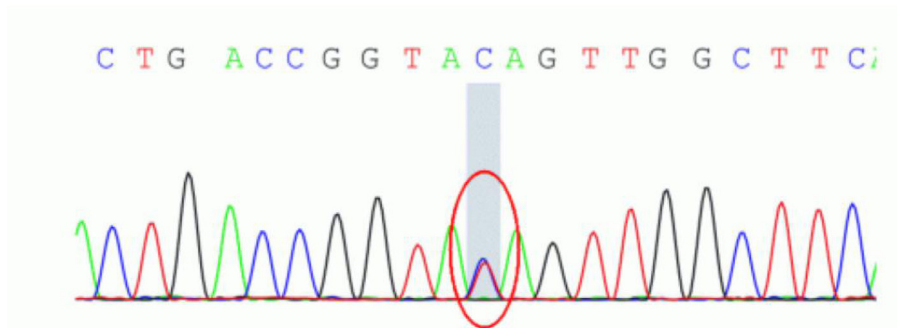
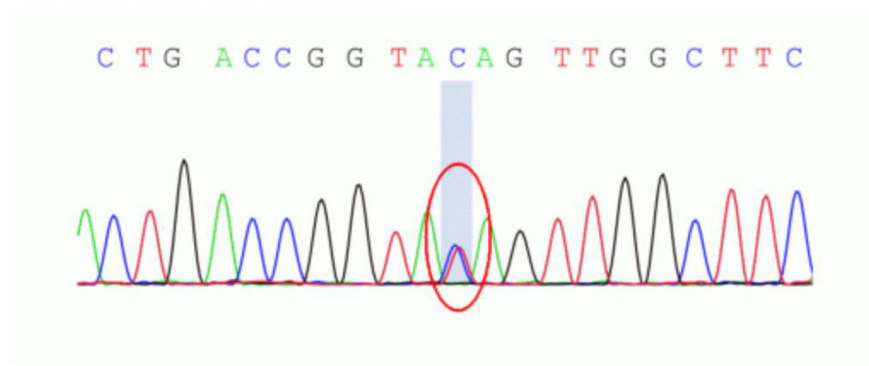
#### *The relationship between the *SORL1* gene and AD*

A meta-analysis showed a significant relationship between *SORL1* polymorphisms and susceptibility to AD [8]. Replicated genetic studies have found that the genetic variation of the *SORL1* gene is associated with AD. Exome sequencing performed in 14 autosomal dominant EOAD index cases found that in 5 patients, the *SORL1* gene harbored unknown, nonsense, or missense mutations [9]. *SORL1* variants in EOAD are rare [10]. AD is an autosomal dominant disease, that is, a single allele mutation can increase the risk of AD. Exon 25 heterozygous mutations in an *SORL1* gene, which are located on chromosome 11, were detected in our patient and his children. Specifically, a missense mutation, substitution of guanine with an adenine at gene loci 3575, caused an amino acid substitution from cysteine to tyrosine on the protein polypeptide chain. *SORL1* gene encodes sorLA or LR11. SorLA is a key protein involved in the processing of the amyloid-beta ( $A\beta$ ) precursor protein (APP) and the secretion of the  $A\beta$  peptide, the aggregation of which triggers AD pathophysiology [11]. LR11 protects APP from being directed to the endosome, where it would be cleaved by beta-secretase producing  $A\beta$ , an important component in the pathophysiological pathway of AD [12].

The patient had a c.3575G>A heterozygous mutation of chr11-121448104.C1192Y (shown below).



His son and daughter had the same c.3575G>A heterozygous mutation of chr11-121448104.C1192Y (as shown below).



**Fig. 2 – An SORL1 gene mutation, c.3575G>A (chr11:121448104), was detected in the patient and his children. This mutation would result in amino acid alteration p.C1192Y.**

The dysfunction of LR11 has been shown to lead to amyloidogenesis. As we know, there is no report of this mutation in patients with EOAD. Multiple genes such as the SORL1 gene, opioid receptor genes, and apolipoprotein E4 (ApoE4) gene have been implicated in the risk of AD. Previous studies have suggested that opioid receptor genes may be used as potential methylation biomarkers for the diagnosis of AD [13]. Individuals carrying the ApoE4 gene have a major genetic risk factor for LOAD [14]; we did not find ApoE4 in the genotype of our patient. Since we did not find any other cause of dementia, and the same heterozygous mutation was found in both his son and daughter, the mutation may have been pathogenic

and could have increased the risk of AD. Further work should investigate the contribution of this heterozygous mutation to EOAD.

#### **MRI characteristics of EOAD**

Pathological changes in the AD brain include diffuse brain atrophy (especially in the hippocampus and temporal, parietal, and prefrontal lobes) and abnormal enlargement of the third and lateral ventricles. These pathological changes are aggravated by the progression of the disease. Polymorphism of the SORL1 gene can affect gray matter atrophy in AD-associated

brain areas or even in the whole brain [4]. This is related to the extensive expression of *SORL1* in the cerebral cortex, hippocampus, and cerebellar hemisphere neurons [15]. The hippocampus of healthy young people carrying the *SORL1* risk gene begins to atrophy and may progress to AD [12] in the future. The earliest characteristic change in AD may be the progressive atrophy of the medial temporal lobe, and hippocampal atrophy is considered the best marker of mild cognitive impairment progressing to AD dementia. Our patient presented with whole-brain atrophy (especially in the bilateral medial temporal lobe and hippocampus), which is consistent with the above report [4,16]. Compared with patients with LOAD, the neuroimaging features of patients with EOAD include more hippocampal sparing and posterior neocortical atrophy, an increased tau burden, and more connectivity changes affecting frontoparietal networks than the default mode network.

In conclusion, the possibility of EOAD should be considered in patients younger than 65 years who present with a significant decline in executive and speech functions (with/without obvious memory impairment). Atrophy of the bilateral medial temporal lobe/hippocampus on MRI may be an important marker for EOAD. An *SORL1* gene mutation, c.3575G>A (chr11:121448104), may increase the risk of AD.

---

### Patient consent statement

Written, informed consent for the publication of this case was obtained from the patient.

---

### Acknowledgments

We would like to thank Editage [www.editage.cn] for English language editing.

---

### REFERENCES

- [1] Mendez MF. Early-onset Alzheimer disease. *Neurol Clin* 2017;35:263–281. doi:10.1016/j.ncl.2017.01.005.
- [2] Joubert S, Gour N, Guedj E, et al. Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment. *Cortex* 2016;74:217–232. doi:10.1016/j.cortex.2015.10.014.
- [3] Alberici A, Benussi A, Premi E, et al. Clinical, genetic, and neuroimaging features of early onset Alzheimer disease: the challenges of diagnosis and treatment. *Curr Alzheimer Res* 2014;11:909–917. doi:10.2174/1567205011666141107151606.
- [4] Shen J, Yu C. *SORL1* gene polymorphisms: genetic, image and behavioral research status. *Int J Med Radiol* 2017;40:411–413 455.
- [5] Mendez MF. Early-onset Alzheimer disease and its variants. *Continuum (Minneapolis, Minn)* 2019;25(1):34–51. doi:10.1212/CON.0000000000000687.
- [6] Mendez MF. Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD. *Arch Med Res* 2012;43:677–685. doi:10.1016/j.arcmed.2012.11.009.
- [7] Palasí A, Gutiérrez-Iglesias B, Alegret M, et al. Differentiated clinical presentation of early and late-onset Alzheimer's disease: is 65 years of age providing a reliable threshold? *J Neurol* 2015;262:1238–1246. doi:10.1007/s00415-015-7698-3.
- [8] Cong L, Kong X, Wang J, et al. Association between *SORL1* polymorphisms and the risk of Alzheimer's disease. *J Integr Neurosci* 2018;17:185–192. doi:10.31083/JIN-170051.
- [9] Pottier C, Hannequin D, Coutant S, et al. High frequency of potentially pathogenic *SORL1* mutations in autosomal dominant early-onset Alzheimer disease. *Mol Psychiatry* 2012;17:875–879. doi:10.1038/mp.2012.15.
- [10] Verheijen J, Van den Bossche T, van der Zee J, et al. A comprehensive study of the genetic impact of rare variants in *SORL1* in European early-onset Alzheimer's disease. *Acta Neuropathol* 2016;132:213–24. doi:10.1007/s00401-016-1566-9.
- [11] Champion D, Charbonnier C, Nicolas G. *SORL1* genetic variants and Alzheimer disease risk: a literature review and meta-analysis of sequencing data. *Acta Neuropathol* 2019;138:173–86. doi:10.1007/s00401-019-01991-4.
- [12] Louwersheimer E, Ramirez A, Cruchaga C, et al. The influence of genetic variants in *SORL1* gene on the manifestation of Alzheimer's disease. *Neurobiol Aging* 2015;36:1605 e13-20. doi:10.1016/j.neurobiolaging.2014.12.007.
- [13] Xu C, Liu G, Ji H, et al. Elevated methylation of *OPRM1* and *OPRL1* genes in Alzheimer's disease. *Mol Med Rep* 2018;18:4297–302. doi:10.3892/mmr.2018.9424.
- [14] Halliday MR, Rege SV, Ma Q, et al. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J Cereb Blood Flow Metab* 2016;36:216–27. doi:10.1038/jcbfm.2015.44.
- [15] Andersen OM, Rudolph IM, Willnow TE. Risk factor *SORL1*: from genetic association to functional validation in Alzheimer's disease. *Acta Neuropathol* 2016;132:653–665. doi:10.1007/s00401-016-1615-4.
- [16] Bralten J, Arias-Vásquez A, Makkinje R, et al. Association of the Alzheimer's gene *SORL1* with hippocampal volume in young, healthy adults. *Am J Psychiatry* 2011;168:1083–1089. doi:10.1176/appi.ajp.2011.10101509.