A novel granulin mutation in logopenic variant primary progressive aphasias: Case report and literature review

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Case Report

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Abstract

Background Primary progressive aphasias (PPA) can be divided into 3 main variants, nonfluent/agrammatic, semantic, and logopenic variant. Logopenic variant PPA (lvPPA) was the third to be described clinically. Majority of these PPA patients harbored mutations in the granulin (GRN) gene on chromosome 17q21.

Case presentation Based on the reported patient’s clinical and neuroimaging data, we considered a diagnosis of lvPPA, characterized by impaired single-word retrieval in spontaneous speech and naming, and impaired repetition of sentences and phrases, with relatively preserved single-word comprehension, object knowledge, motor speech, and no speech errors in spontaneous speech or naming. MRI of head revealed marked lateral atrophy in the left parietal cortex and a gradual change over a period of six years. A heterozygous 10-bp frameshift deletion (C.274_283del ATGCGGGGAT) was identified in exon 4 of the GRN gene (NM_002087.4), leading to alteration of cysteine to alanine at amino acid 92 and creation of a premature stop codon at position 161. This GRN associated lvPPA presentation is rarely previously reported.

Conclusions We summarized clinical, MRI and genetic features of an lvPPA individual carried a novel GRN mutation. We have provided a clue for exploring the pathogenicity significance of GRN mutation in frontotemporal lobar degeneration (FTLD), which broadens the genetic and phenotypic spectrum of FTLD.

Background

The primary progressive aphasias (PPA) is a heterogeneous item of focal ‘language-led’ dementias that pose substantial challenges for diagnosis and management. According to clinical manifestations, imaging examination and definite pathology if pathologic or genetic data are available, PPA can be divided into 3 main variants, nonfluent/agrammatic, semantic, and logopenic variant. Logopenic variant PPA (lvPPA) was the third to be empirically described clinically by Gorno-Tempini et al in 2004. Current data show that most PPA patients exhibit tau-positive, ubiquitin/TDP43-positive frontotemporal lobar degeneration (FTLD) pathology, or Alzheimer disease (AD) pathology. Approximately 69% of lvPPA cases are reported to be associated with amyloid pathology, followed by 18% with FTLD pathology. Imaging findings in lvPPA include predominant left posterior perisylvian or parietal atrophy on MRI, as well as predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on single photon emission computed tomography (SPECT) or positron emission tomography (PET). Koedam scores can be used to divide parietal lobe atrophy levels. However, the specific pathogenesis of lvPPA is still unclear.

PPA can be inherited in an autosomal dominant manner, and the majority of these patients harbored mutations in the granulin (GRN) gene on chromosome 17q21 in west. Progranulin (PGRN), a 593-amino acid multifunctional protein encoded by the GRN gene, plays a key role in the development, survival, function, and maintenance of neurons and microglia in the mammalian brain, and may be considered as
a therapeutic target in neurodegenerative diseases such as AD, Parkinson's disease (PD), and limbic-predominant age-related transactivation response DNA-binding protein 43 encephalopathy\textsuperscript{11}. \textit{GRN} loss-of-function mutations cause neuronal ceroid lipofuscinosis or frontotemporal dementia-GRN (FTD-GRN) in a gene dosage-dependent manner\textsuperscript{12}. LvPPA was the most frequent linguistic variant (41%), followed by nonfluent/agrammatic (28%) and mixed forms (25%), and semantic variant was rather rare (6%) in PPA amyloid-negative patients carried \textit{GRN} mutations \textsuperscript{13}. Although the majority of lvPPA presented with AD pathology based on the post mortem neuropathological brain tissue examination and biomarker analysis of cerebrospinal fluid, amyloid PET, and/or blood\textsuperscript{8}, but nearly 50% PiB-negative lvPPA patients were \textit{GRN}-positive, who were on average 8 years younger, and had lower PiB-PET ratios compared to GRN-negative patients\textsuperscript{14}.

In this study, we report a novel \textit{GRN} mutation in a Chinese patient with lvPPA. We also summarize the genetic and clinical features of all Chinese patients with \textit{GRN} mutations reported in the literature to date. Characteristic Magnetic Resonance Imaging (MRI) changes and progression of lvPPA are displayed.

**Case presentation**

Clinical and neuropsychological workup

The patient was a 77-year-old woman with 14 years of education who used to work as a community worker. She had a progressive course of disease, right-handed, arrived at the Neurology ward of Changzhou No.2 People's Hospital Affiliated to Nanjing Medical University in Changzhou City, presented with a 3-year history of speech disorder. Three years ago, she had no obvious inducement to appear speech disorder, manifested as poor language expression ability, lack of speech, difficulty in finding words, unable to name, the words fail to convey the meaning, speech errors in spontaneous speech and naming according the description of her son. But language comprehension was relatively preserved, she could engage in simple housework and take care of herself. Half a year ago, she gone out and can't find the way home, easy to be suspicious of others, memory showed a progressive decrease, placed things can not find all the time along with agraphia. She showed no exertion of lifting limbs, no dragging of lower limbs, no obvious slowness of movement, no hallucinations, no abnormal mental behavior, no diplopia, blurred vision, no dysphagia, coughing when drinking water, no limb convulsions, no confusion. In June 2022, the patient went to the outpatient clinic of our hospital for head MRI, which showed that the left parietal and temporal lobe was atrophied and the left paracele was dilated compared with the right. The patient took some drugs such as donepezil, citicoline, and oxiracetam. The patient now had a progressive deterioration in verbal expression, few solid words in spontaneous speech, an inability to name daily necessities, and difficulty repeating words, sentences and phrases.

The patient's family pedigree is shown in Figure. 1. Her father developed “dementia” at the age of 65 years and died at 70 years, her youngest brother developed “dementia” at 60 years and died at 65 years. No other family member had a history of dementia, motor dysfunction, or neurodegenerative diseases.
The patient had a 3-years history of hashimoto thyroiditis, and was currently using unimethylate. T3, T4, and TSH were all in the normal range.

Her performance was remarkable for impaired single-word retrieval in spontaneous speech and naming, as well as impaired repetition of sentences and phrases. Although she could understand words and sentences, she was unable to communicate with others, often saying irritably “I used to be fine”. Physical examination of the nervous system showed her right upper limb swinging less than the right side when walking, but there were no other positive physical findings. The patient's neuropsychological test scores were as follows: MMSE 2, MoCA 1, CDR 1 and ADL 30. The language impairment was assessed using a language assessment scale suitable for Chinese people - aphasia battery of Chinese(ABC). The scale consists of four sub-items, including spontaneous speech (information content and fluency), listening comprehension, paraphrasing, and naming. In the four test items, the patient scored the highest in listening comprehension, “Yes or No” questions were answered correctly 80%, the verbal command was 50%, and the listening comprehension was 20%. Her scores on the other three sub-items were below 50%.

**Neuroimaging**

MRI of her head revealed marked lateral atrophy in the left parietal cortex (Figure. 2). On brain MRI in 2017, only the left parietal lobe was atrophied with mild widening of posterior cingulate and parieto-occipital sulci classified as Koedam score grade 1, and other cerebral lobes were not significantly atrophied. The atrophy of the parietal lobe gradually progressed, with substantial sulcal widening rated Koedam grade 2 in 2020. By 2022 there was extreme posterior cingulate and parieto-occipital sulcal dilation, Koedam grade 3. Since 2020, the atrophy of the temporal and frontal lobes could be observed in addition to the parietal atrophy.

Based on the patient's clinical and neuroimaging data, we considered a diagnosis of IvPPA², characterized by impaired single-word retrieval in spontaneous speech and naming, and impaired repetition of sentences and phrases, with relatively preserved single-word comprehension, object knowledge, motor speech, and no speech errors in spontaneous speech or naming. MRI of head revealed marked lateral atrophy in the left parietal cortex and a gradual change over a period of six years.

**GRN gene**

Whole exome sequencing was performed on the DNA of patient's peripheral blood. We examined gene mutations associated in AD, FTD, or other dementiaredrelated neurodegenerative diseases. A heterozygous 10-bp frameshift deletion (C.274_283del ATGCGGGGAT)was identified in exon 4 of the GRN gene (NM_002087.4), leading to alteration of cysteine to alanine at amino acid 92 and creation of a premature stop codon at position 161 (Figure. 3). Regrettably, genetic testing could not be performed on her deceased brother who had similar symptoms, and testing was declined by her niece. There were no additional disease-causing mutations in additional screened genes. This GRN deletion was absent from the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Genome Aggregation Database (gnomAD; https://gnomad.
Discussion and Conclusion

PPA is an umbrella term which predominantly affect language processing, and lvPPA with the remarkable clinical features of impaired single-word retrieval in spontaneous speech and naming and impaired repetition of sentences and phrases, predominant left parietal atrophy on MRI \(^2\). Due to differences in language and anatomy, our patient mainly presented with features consistent with lvPPA. Parkinsonian symptoms are uncommonly described in PPA. Extensive atrophy of the left hemisphere spread to the basal ganglia of the brain results in the patient's right upper limb swinging less than the right side when walking. Apraxia from parietal lobe atrophy cannot be excluded. As a major pathogenic gene of FTLD, GRN carriers have the largest clinical phenotypic variation, which does not rule out the possibility of neurodegenerative movement disorder phenotypes like corticobasal ganglia degeneration syndrome.

The patient had significantly increased anti-thyroid peroxidase antibodies and a clear diagnosis of Hashimoto's thyroiditis. Hashimoto's encephalopathy can cause symptoms such as cognitive decline\(^1^5\), but it is global, not just impairing the language threshold. The main clinical feature in this patient was predominant language impairment, without altered consciousness, confusion, seizures, or extrapyramidal signs that may point toward Hashimoto's encephalopathy. While brain hypoperfusion or hypometabolism on SPECT are sometimes seen with Hashimoto's encephalopathy, the degree of focal atrophy on MRI in this case would be atypical\(^1^6\). Therefore, her language presentation is less likely attributable to Hashimoto's encephalopathy.

At the time of this visit, because the patient was unable to clearly describe age of onset and process of the disease, so her son provided the history. Family members firstly noticed speech abnormalities starting around 2020, but the patient had head MR examined in 2017, and the left parietal lobe was atrophy with mild widening of posterior cingulate and parieto-occipital sulci classified as Koedam score grade 1, which suggests the disease process likely started before 2017. The atrophy of the left parietal lobe in this patient gradually grievous by 2020, the left temporal and frontal lobes also showed imaging atrophy. The sequential changes on MRI over 6 years provide valuable documentation of the progression in this case.

GRN mutations are common in western countries, accounting for 34.6% of mutations in patients with FTD\(^1^7\), but GRN mutations are rare in China\(^1^8\), with a prevalence of just 1.2–2.6%\(^1^9\). Microtubule-associated protein tau(MAPT) and coiled-coil-helix-coiled-coil-helix-domain(CHCHD10) gene may be the major genes affecting Chinese patients with FTLD\(^2^0\). More than 70 pathogenic GRN mutations have been identified\(^2^1\). The main clinical manifestations of GRN-FTLD were bvFTD, followed by nfvPPA and svPPA. This GRN associated lvPPA presentation has not been previously reported in China. We also identified a novel 10-bp deletion (c.274_283 ATGCGGGAT) in exon 4 of GRN, leading to a cysteine to alanine
substitution at amino acid 92 and creation of a premature stop codon at position 161. We also summarized all GRN mutations with FTLD reported in China, of which phenotypes include bvFTD, PPA, corticobasal ganglia syndrome, atypical PD and amyotrophic lateral sclerosis\(^1\)\(^9\) (Figure. 4). The higher prevalence of GRN mutations in female versus male FTD patients suggests sex-related factors may modulate phenotypic expression.\(^2\)\(^2\)

LvPPA is most often associated with AD pathology, followed by FTLD pathology\(^7\),\(^2\)\(^3\). Among all the relevant gene mutations of lvPPA, GRN has the highest mutation rate 4.36%, in addition to PSEN1, TREM2 and MAPT gene mutations explored\(^8\), though data are limited. Here we report a novel GRN gene mutation associated with lvPPA. In carriers of GRN mutations, under-connectivity in the left frontal parietal grid and hyperconnectivity within the executive grid have been verified\(^2\)\(^4\). Parietal grid damage is still an early imaging signature of GRN-associated FTLD\(^7\). These are consistent with the clinical manifestations of our patient, On MRI in 2017, only the left parietal lobe atrophy was observed, and gradually the left frontal and temporal lobes atrophy were appeared as the disease progressed.

Our study had some limitations. First, we lacked estimates of amyloid positivity prevalence typically defined by PET or cerebrospinal fluid biomarkers. Second, there may have publication bias in our literature review, because genetic screening is not common in some rural areas of China. Larger multicenter genetic studies are needed to confirm the frequency of GRN mutations in China.

We summarized clinical, MRI and genetic features of an lvPPA individual carried a novel GRN mutation, and this GRN-related lvPPA phenotype of this patient firstly reported in China. We have provided a clue for exploring the pathogenicity significance of GRN mutation in FTLD, which broadens the genetic and phenotypic spectrum of FTLD. However, we cannot identify Cys92Alafs mutation as completely responsible for lvPPA due to no functional data for this patient.

**Declarations**

**Ethics approval and consent to participate**

Ethical approval was obtained from the ethics committee of Changzhou No.2 People's Hospital Affiliated to Nanjing Medical University. Written informed consent for publication was obtained from the guardian. All methods were carried out in accordance with relevant guidelines and regulations.

**Consent for publication**

Written informed consent for publication of her clinical details and clinical images was obtained from the guardian of the patient. A copy of the consent form is available for review by the Editor of this journal. Parental/Guardian provided informed consent for publication.

**Availability of data and materials**
Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Sha-sha Jia collected the data, wrote the original draft. Sha-sha Jia, Pu-lei Li and Ping-Gao diagnosed and treated the patient. Ye Jiang and Cheng-liang Zhang carried out neuropsychological tests. Wen-wei Yun had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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**Authors' information (optional)**

Not applicable.

**References**


Figures
Figure 1

Pedigree of the patient's family.
Figure 2

Neuroimaging of the patient with GRN mutation. A) MRI showing left-side atrophy in the parietal lobes in 2017 with mild widening of posterior cingulate and parieto-occipital sulci classified as Koedam score grade 1; B) The atrophy of the parietal lobe gradually increases with substantial widening of the sulci classified as Koedam score grade 2 in 2020; C,D) extreme widening of the posterior cingulate and parieto-occipital sulci classified as grade 3 in 2022 and 2023.
Figure 3

Chart and electropherograms of Sanger sequencing of PCR products showing the novel GRN mutation [c.273_282del:p.Cys92Alafs.] compared with normal individuals in the bottom panel.

Figure 4
Diagrammatic representation of the human GRN gene, PGRN protein and its proteolytic digestion pathway to GRN peptide because of the c.273_282del (p.Cys92Alafs) mutation in exon 4. GRN schematic structure include 12 coding exons (green boxes) and UTR. 12 GRN mutations reported in China so far. The c.273_282del (p.Cys92Alafs) mutation identified in this study is indicated in red. The PGRN protein include 593-amino acid. The blue lettered boxes represent individual granulin modules. The thin lines descending from the GRN gene schematic structure indicate which exons contribute to which protein modules. The bottom line illustrates the cleavage of PGRN into granulin peptides with premature termination of the coding sequence resulting from 10-bp(ATGCGGGGAT) deletion in the coding region, No. 92 amino acid mutates from cysteine to alanine and creates a new reading frame, resulting in the termination of amino acid No. 161 in exon 4 of the GRN gene.