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CASE REPORT

Idiopathic basal ganglia calcification associated with new *MYORG* mutation site: A case report

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Author contributions: Fei BN collected the clinical data and was the major contributor in writing the manuscript; Su HZ and Yao XP performed the genetic analysis; all authors read and approved the final manuscript; Ding J and Wang X were the patient's attending physicians and directed the writing of the article.

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Abstract

BACKGROUND

Idiopathic basal ganglia calcification (IBGC) is a neurodegenerative disease characterized by symmetrical calcification of basal ganglia and other brain region, also known as Fahr's disease. It can be sporadic or familial, and there is no definite etiology at present. With the development of neuroimaging, the number of reports of IBGC has increased in recent years. However, due to its hidden onset, diverse clinical manifestations, and low incidence, it is likely to be misdiagnosed or ignored by potential patients and their family.

CASE SUMMARY

We report a case of a 61-year-old man who presented with symptoms of dysphagia and alalia. His computed tomography scan of the brain revealed bilateral symmetric calcifications of basal ganglia, cerebellum, thalamus, and periventricular area. The genetic test showed a new mutation sites of *MYORG*, c.1438T>G mutation and c.1271_1272 TGGTGCGC insertion mutation. He was finally diagnosed with IBGC.

CONCLUSION

It is important to detect *MYORG* mutation when IBGC is suspected, especially in those without an obvious family history, for better understanding of the underlying mechanism and identifying potential treatments.

Key Words: Idiopathic basal ganglia calcification; Fahr's disease; Gene; Point mutation; Inheritance; Case report

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Core Tip: Idiopathic basal ganglia calcification (IBGC) is characterized by calcification of basal ganglia and other regions of the brain. IBGC is clinically heterogeneous and usually exhibits an autosomal dominant pattern of inheritance. We report a case of a 61-year-old man who presented with symptoms of dysphagia and alalia. His computed tomography scan of the brain revealed bilateral symmetric calcifications of basal ganglia, cerebellum, thalamus, and periventricular area. The genetic test showed a new mutation site of *MYORG*.

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INTRODUCTION

Idiopathic basal ganglia calcification (IBGC) is characterized by calcification of basal ganglia and other regions of the brain, commonly known as Fahr's disease[1]. IBGC is clinically heterogeneous and usually exhibits an autosomal dominant pattern of inheritance. Wang *et al*[2] discovered the first pathogenic gene of IBGC: *SLC20A2* in 2012. Three other IBGC pathogenic genes (*PDGFRB*[3], *PDGFB*[4], and *XPR1*[5]) were subsequently identified. In 2018, Yao *et al*[6] first reported that *MYORG* is a new pathogenic gene for IBGC with an autosomal-recessive trait. Here, we report a family with novel mutation sites of *MYORG*.

CASE PRESENTATION

Chief complaints

The patient is a 61-year-old man with the complaint of progressive severe dysphagia and alalia.

History of present illness

Patient's symptoms started 4 years ago and were getting worse. He denied any headache, seizures, and psychiatric symptoms.

History of past illness

Patient has hypertension for more than 10 years.

Personal and family history

Patient's parents passed away in their sixties with unknown reason. He had an old brother and three old sisters, three of them died of unknown reason. The surviving sister is clinically asymptomatic but has calcifications on computed tomography (CT) scan (Figure 1A), and total calcification[7] score was 10. His three daughters were also asymptomatic and with normal CT scan. The pedigree chart is shown in Figure 2.

Physical examination

The neurological examination was normal.

Laboratory examinations

Laboratory tests, including serum calcium, phosphorus, and parathyroid hormone levels, were within normal limits (calcium 2.22 mmol/L, phosphorus 0.84 mmol/L, parathyroid hormone 37.5 ng/L).

Imaging examinations

Patient's CT scan revealed multiple symmetric calcifications of bilateral basal ganglia,

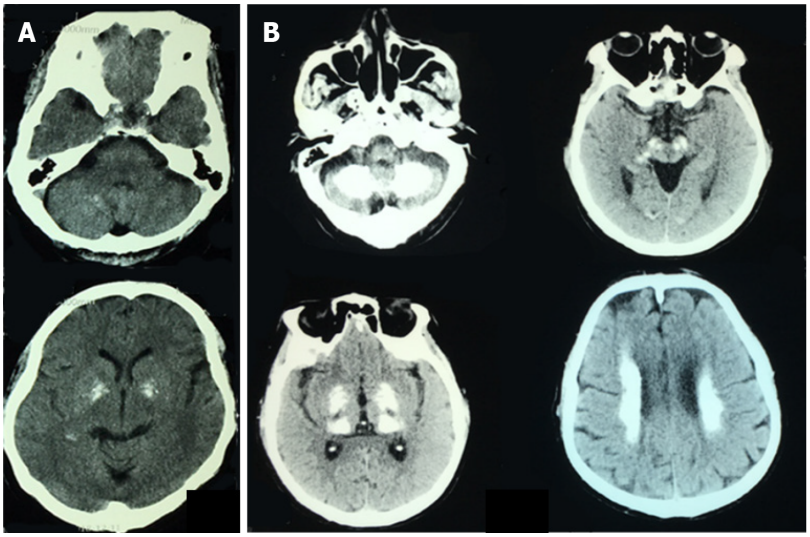

Figure 1 Computed tomography. A: Basal ganglia and cerebellum calcification of patient's sister; B: Patient's symmetric calcifications of bilateral basal ganglia, cerebellum, thalamus, and periventricular area.

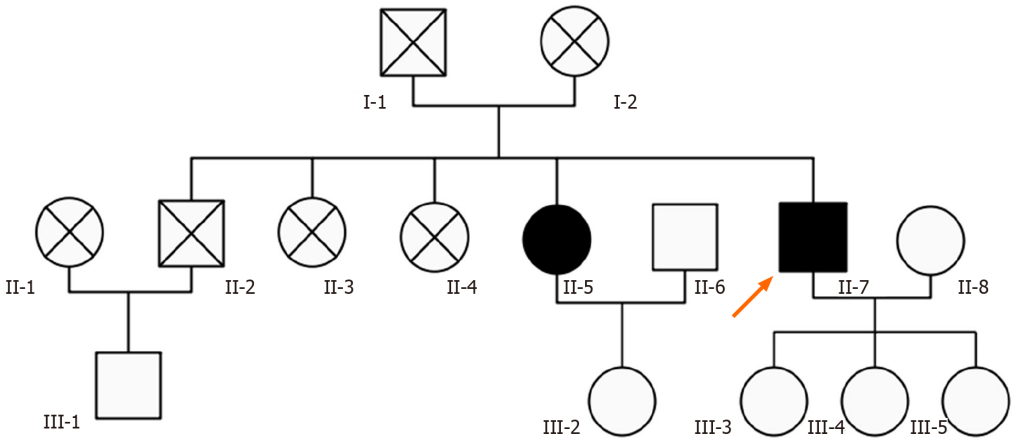

Figure 2 Pedigree. The patients with idiopathic basal ganglia calcification are represented in black, unaffected individuals in white. The index patient is indicated by an arrow.

cerebellum, thalamus, and periventricular area (Figure 1B). Total calcification score was 54.

Genetic tests

Genetic tests were done for the patient and his family. Excluding the dead and unreachable individuals, 7 people over two generations of the patient's family were investigated. The patient's genetic test showed c.1438T >G mutation and c.1271_1272 TGGTGCGC insertion mutation in exon 2 of *MYORG* gene. Besides the patient, his sister and two of his daughter have *MYORG* c.1438T>G mutation, while one daughter has *MYORG* c.1271_1272 TGGTGCGC insertion mutation (Table 1 and Figure 3).

FINAL DIAGNOSIS

According to these laboratory tests and neuroimaging, he was diagnosed with IBGC.

TREATMENT

Oxiracetam and nicergoline were given for neurotrophic treatments and improving cerebrovascular circulation.

Table 1 Clinical characteristics of pedigree

	II-5	II-7	II-8	III-1	III-3	III-4	III-5
Age at evaluation	66	61	61	51	36	34	32
Education level	II	II	II	III	IV	IV	IV
MMSE (/30)	27	26	28	29	30	30	30
MoCA (/30)	26	19	27	28	30	29	29
Clinic symptom	-	+	-	-	-	-	-
Calcifications on CT	+	+	-	-	-	-	-
Total calcification score	54	10	0	0	0	0	0
MYORG mutation	+	+	-	-	+	+	+
c.1438T>G mutation	-	+	-	-	-	-	+
c.1271_1272 TGGTGCGC insertion mutation	+	+	-	-	+	+	-

CT: Computed tomography; MMSE: Mini-mental state examination; MoCA: Montreal Cognitive Assessment.

OUTCOME AND FOLLOW-UP

The symptoms were not approved with these agents.

DISCUSSION

IBGC is a hereditary disease of the nervous system. With the wide application of CT, the detection rate of IBGC becomes higher and higher. Most patients were healthy in the adolescent period. Even if characteristic calcification lesions had appeared in the head CT examination, there might not be obvious abnormal symptoms of the nervous system. Neuropsychiatric and motor disorders would gradually present in the middle-aged and elderly patients with progressive parkinsonism and spasticity.

In this pedigree, the patient had compound heterozygous mutations, one point mutation and one insertion mutation. His sister and daughters only had one mutation site, and they did not present with any symptoms. Some research found that homozygotes have more serious brain calcification, whereas with the heterozygous mutation, only punctated calcification was found in the globus pallidus. The clinical symptoms in homozygotes are various neurological symptoms, while heterozygotes are usually clinically asymptomatic[8]. Although the patient's sister and daughters are asymptomatic, they had the *MYORG* mutation. We suggested to them annual cranial CT scans, because with age the disease may progress and clinical symptoms may appear.

Previous studies reported that IBGC is inherited as an autosomal dominant disease [9,10] and identified *SLC20A2* coding for the phosphate transporter PiT2, *PDGFRB*[3] coding for the platelet derived growth factor receptor, as a cause of IBGC. However, *SLC20A2*, *PDGFRB*, *PDGFB*, and *XPR1* mutations were only detected in 16.8% of familial brain calcification. The underlying reason of IBGC remains unclear, especially in those without a prominent family history. In 2018, Yao *et al*[6] identified *MYORG* as the new recessive causal gene for IBGC, and reported 10 different mutation sites. Our patient and his family have *MYORG* novel mutation sites, c.1438T>G mutation and c.1271_1272 TGGTGCGC insertion mutation, which have not been reported previously.

MYORG, also known as KIAA1161 or NET37, is located on chromosome 9p13.3. It encodes a protein containing 714 amino acids, which is a member of the glycosylase 31 family. *MYORG* gene was specifically expressed in S100b positive astrocytes. Bilateral symmetrical nodules of cerebral calcification were observed in *MYORG* knockout mice. The main components of calcium nodules were calcium and phosphorus, which were highly similar to the elements of brain calcification in clinical patients, which proved that *MYORG* autosomal recessive function deletion mutation was an important pathogenic gene of IBGC. The mutation of this gene causes dysfunction of astrocytes, which may affect the combination of astrocytes and pericytes, interfere with the

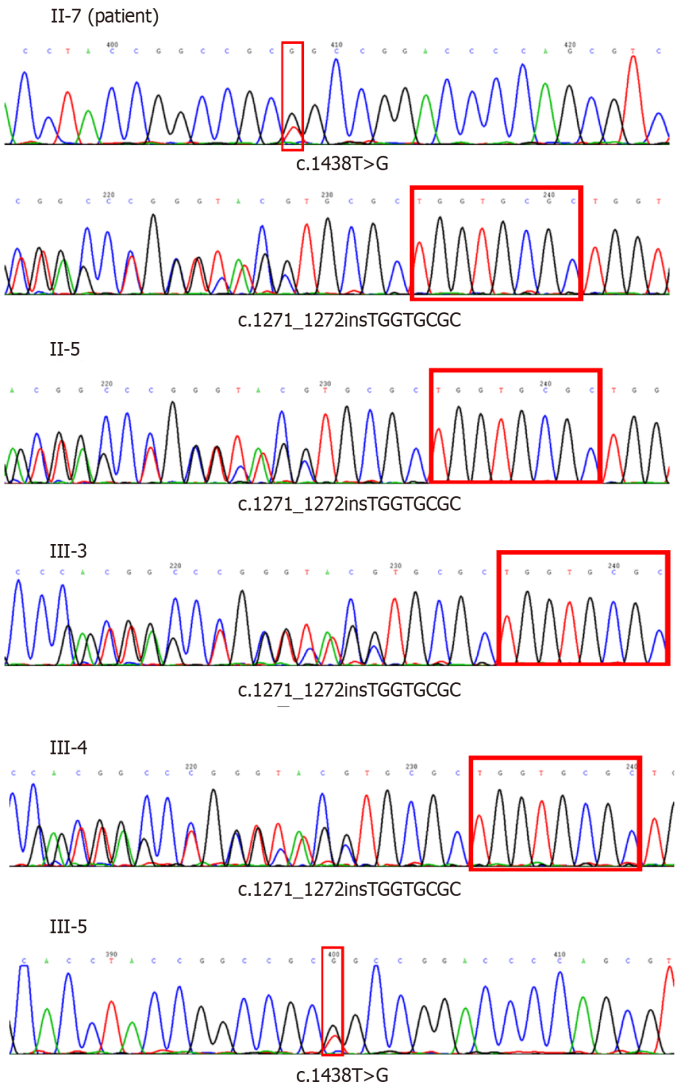

Figure 3 Gene sequencing. II-7 (patient) has c.1438T>G mutation and c.1271_1272 TGGTGCGC insertion mutation. II-5, III-,3 and III-4 has c.1271_1272 TGGTGCGC insertion mutation. III-5 has c.1438T>G mutation.

normal function of neurovascular unit, and finally may lead to the calcification of the brain. According to the clinical manifestations, Chen *et al*[11] found that 76.5% patients with *MYORG* mutation were symptomatic, and the most recurrent symptom was movement disorder. Our patient's manifestation was progressive dysphagia and alalia.

CONCLUSION

Since many patients will exhibit a progressive neurological disorder with no known treatment, it is important to detect *MYORG* mutation, especially in those without obvious family history, for better understanding the underlying mechanism and identifying potential treatments.

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