Original Article

A Novel *SLC20A2* Mutation Associated with Familial Idiopathic Basal Ganglia Calcification and Analysis of the Genotype-Phenotype Association in Chinese Patients

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Abstract

Background: Idiopathic basal ganglia calcification (IBGC) is a genetic disorder characterized by bilateral basal ganglia calcification and neural degeneration. In this study, we reported a new *SLC2OA2* mutation of IBGC and reviewed relevant literature to explore the association between phenotypes and genotypes in Chinese IBGC patients.

Methods: Clinical information of the proband and her relatives were collected comprehensively. Blood samples of both the patient and her father were obtained, and genetic screening related to IBGC was performed using second generation sequencing with their consent. Findings were confirmed by Sanger sequencing. Polyphen-2 was used to predict the potential association between mutations and disease. Then, we retrieved literatures of Chinese IBGC patients and explored the association between phenotype and genotype.

Results: A novel mutation was identified through genetic testing, and it is suggested to be a damage mutation predicted by Polyphen-2. Through literature review, we found that *SLC20A2* mutation is the most common cause for IBGC in China. Its hot spot regions are mainly on the 1st and 8th exons; the second common one is PDGFB where the hot spot covered a length of 220–230 bp localized on the 2nd exon; moreover, Chinese IBGC patients featured early-onset, more severe movement disorder and relatively mild cognitive impairment compared with those in other countries.

Conclusions: There is significant heterogeneity both in phenotype and genotype in Chinese IBGC patients. Further research of pathogenic mechanism of IBGC is required to eventually develop precise treatment for individuals who suffered this disease.

Key words: Genotype; Idiopathic Basal Ganglia Calcification; Phenotype; *SLC20A2*

Introduction

Idiopathic basal ganglia calcification (IBGC) is an autosomal dominant inherited disease characterized by neural degeneration and basal ganglia calcification. IBGC is clinically heterogeneous, manifesting a variety of symptoms including but not limited to movement disorders, cognitive impairment, and psychiatric symptoms. The radiological features are central neural system calcification mainly affecting bilateral basal ganglia, cerebellar dentate nuclei, and subcortical areas. Pathological findings are calcium accumulation around arteriole and small vessels.[1]

IBGC now has five types, except for children IBGC, others are all adult onset. There are four causal genes identified so far, including solute carrier family 20 member 2 (*SLC20A2*), platelet-derived growth factor receptor beta (*PDGFRB*), platelet-derived growth factor subunit B (*PDGFB*), xenotropic and polytropic retrovirus receptor 1 (*XPR1*).[2] In this study, we reported a familial IBGC pedigree caused by a novel *SLC20A2* mutation. Furthermore, we reviewed literature clinical characteristics of different genotype, aiming to help clinical diagnosis.

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Methods

Ethical approval

All subjects signed informed consent for genetic testing, and the study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, China.

Clinical information collection

Clinical information of the proband was comprehensively collected, including detailed symptoms, family history, physical examination, laboratory tests results, and cranial radiological scan. Some of the family members underwent computed tomography (CT) scan. Battery of routine laboratory tests was performed to exclude other causes of basal ganglia calcification. Family members were considered as affected members when there are similar clinical characteristics and imaging results. Family members lacking clinical characteristics of IBGC and cerebral calcification are considered as probable unaffected members of the family.

Gene sequencing and mutation prediction

Blood samples of both the proband and her father were obtained and genetic testing covering 192 relevant genes was performed. Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) was used to predict possible association between the mutation and disease.

Literature retrieve

We retrieved literatures of IBGC of Chinese patients in PubMed published before October 1, 2017, and analyzed to look for the association between phenotype and genotype, aiming to help clinical diagnosis.

Results

Clinical information

The proband of this pedigree is 52-year-old woman [Figure 1, II-5]. Her chief complaints were as follows paroxysmal tics, progressive memory loss, and bilateral upper limb spasm for 6 months. She was admitted to our hospital on February 15, 2017. Two years ago, she had paroxysmal tics without conscience loss, presenting as limb spasm, which lasted for about 2 min and then relieved by itself. After then, this kind of symptom has never presented again. However, her memory started to decline since then. One year ago, she complained a significant memory loss, such as she could not find household items living stuffs and she had difficulty in finding way home. The symptoms mentioned above continued to worsen. She developed speaking difficulties. In addition, she also experienced muscle tics in her hands lasting about 2 min and then the symptoms alleviated on their own. Ictal frequency was about 2–3 times a week. Consciousness was retained during ictal period.

Physical examination

At the time of her first neurologic examination, the patient was alert and showed significantly impaired memory and calculation. CN: Intact. MOTOR: Muscle bulk and tone are normal. Strength is 5/5 throughout. REFLEXES: Reflexes are 2+ and symmetric. Plantar responses are flexor. SENSORY: Intact. COORDINATION: Slight impairment on heel-to-shin testing.

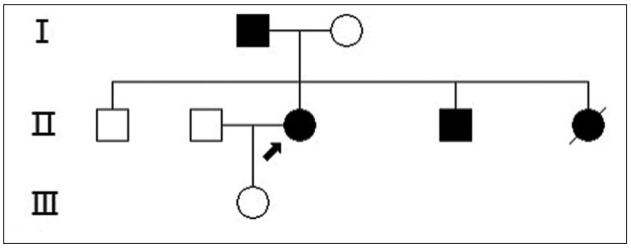

Figure 1: Pedigree of the family, No. 5 is the proband reported.

Laboratory test results

Laboratory tests were performed to exclude other causes of basal ganglia calcification. Serum calcium was 2.21 mmol/L (reference range: 2.03–2.67 mmol/L). Serum phosphorus was 1.32 mmol/L (reference range: 0.84–1.65 mmol/L). Twenty-four hours urine calcium and phosphorus values were normal. Blood parathyroid level was normal. Other laboratory tests including blood routine, biochemistry, immunology, and paraneoplastic tests were within normal ranges. CT scan showed bilateral symmetric basal ganglia calcification [Figure 2b]. We excluded hyperthyroidism and other causes of abnormality of metabolism of calcium and phosphorus.

Pedigree description

Retrieving her family history, we found that her father appeared dementia in his 70s, his CT scan shown bilateral basal ganglia calcification [Figure 2a]. Her mother and elder brother were shown no abnormality. Her little sister died of convulsion in 2 years old; however, there was no positive imaging result left shown she was affected. Her brother presented no symptom while his CT image shown similar calcification lesion in brain. Important information about the proband and other affected and unaffected members is shown in Table 1.

Genetic sequencing and function prediction

Sequencing results of the patients were compared with those of 1000 normal people, and a new *SLC20A2* missense mutation was found, c.248C>T, p.Thr83Met in both her and her father's blood DNA samples. Due to the absence of II-3, II-6 of the family, we could not further confirm cosegregation within the family by genetic sequencing. Instead, we used Polyphen 2 (http://genetics.bwh.harvard.edu/pph2/) to predict the likelihood of this mutation interfering with the normal protein function. Interestingly, it was shown to be probably damaging [Figure 3].

Clinical characteristics of other genotypes

SLC20A2-related IBGC was the most frequent cause in both familial and sporadic IBGC, accounting for about 40–50% in the whole single-gene caused IBGC.[3,4] The typical characteristics of *SLC20A2*-related IBGC patients in the Chinese population including pedigree in this study featured early onset and paroxysmal movement disorder.[5] Cognitive impairment was much milder in most patients compared with

Table 1: Information of each pedigree member

Number	Relation	Diagnosis	Symptoms	Imaging result	Genetic mutation
1	Father	Affected	Dementia	Calcification	c.248C>T
2	Mother	Unaffected	–	–	–
3	Brother	Unaffected	–	–	–
4	Husband	Unaffected	–	–	–
5	Proband	Affected	Cognitive impairment paroxysmal movement disorder	Calcification	c.248C>T
6	Brother	Affected	–	Calcification	–
7	Sister	Probable affected (died)	Convulsion	–	–
8	Daughter	Unaffected		–	–

–: Not applicable.

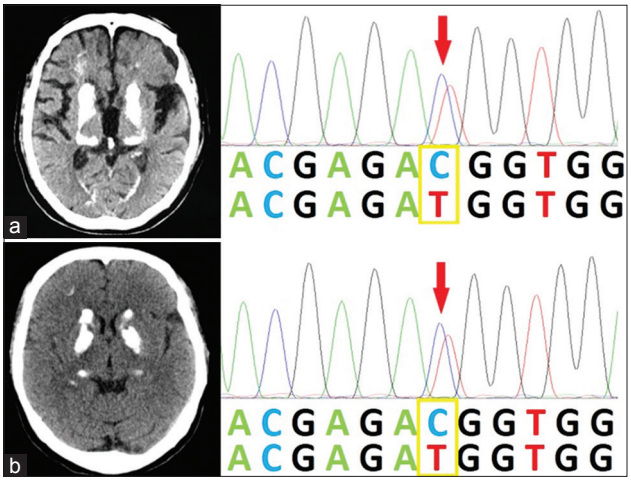

Figure 2: CT scan and genetic findings of the proband and her father. Gene sequencing results show both of them carry the same mutation of *SLC20A2*. (a) Brain CT of the proband's father shows mild extensive brain atrophy bilaterally and symmetrical calcification in bilateral basal ganglia and occipital white matter. Genetic analysis suggests a novel *SLC20A2* heterozygous missense mutation, c.248C>T. (b) Brain CT of the proband shows similar radiological findings, yet with milder calcification. Genetic analysis shows that the proband carries the same *SLC20A2* heterozygous missense mutation. CT: Computed tomography; *SLC20A2*: Solute carrier family 20 member 2.

patients of other counties. As shown in Table 2, there has been reported about 40% mutation found within the 8th exon, the next is the 1st exon, accounting for about 30%.

PDGFB gene was the second cause of single gene IBGC.[10,11] The typical clinical characteristics were much milder compared with those carried *SLC20A2* mutations, which feature movement disorder and atypical symptoms such as headache slight memory decline and mutations of *PDGFB* mainly focused on the region of the 2nd exon covering a length of 220–230 bp [Table 3].

As for other genotypes, there were only 2 *PDGFRB*-positive cases in a screen among Chinese patients of non-*SLC20A2* and non-*PDGFB*.[14] *XPR1*-related IBGC has not found in China yet.

Discussion

In this study, we found a novel *SLC20A2* mutation of IBGC. *SLC20A2*-related IBGC was the most common cause in

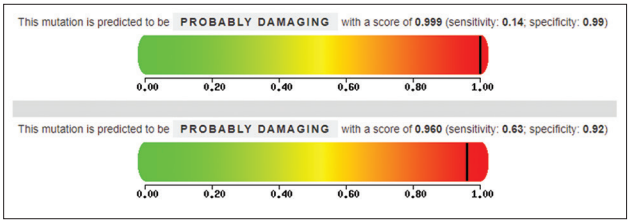

Figure 3: Polyphen-2 functioal prediction results. HumDiv result shows that the mutation is predicted to be probably damaging with a score of 0.999 (sensitivity: 0.14 specificity: 0.99). HumVar result shows that the mutation is predicted to be probably damaging with a score of 0.960 (sensitivity: 0.63 specificity: 0.92).

familial and sporadic IBGC, accounting for about 40–50% of IBGC cases caused by a single gene.[3,4] According to Human Gene Mutation Database, there are 50 mutations in *SLC20A2* associated with IBGC, most of which are localized in the 8th exon.[1,4,5,7-9,15-18] In China, the most frequent single-gene IBGC reported was *SLC20A2*-related IBGC.[5,7-9,18] *SLC20A2* gene encodes for sodium-dependent phosphate transporter 2, a membrane carrier of phosphorus mainly expressed at basal ganglia and cerebellum where calcium accumulation was most significant.[19] The 8th exon encodes for the motif related to binding and transporting phosphate. Mutations leading to amino acid sequence changes might impair the function of phosphate transportation process and cause local/focal extracellular calcification, which is the production of the combination of calcium ion and phosphate deposits.[7,20-22] Local calcification influence not only function of local areas but also function of other related areas through brain connection, which was considered as a plausible mechanism underlying movement disorder and cognitive and psychiatric symptoms seen in patients.[23,24]

Due to the different pathogenicity caused by different types of mutations and resilience ability of individuals, clinical manifestations varied significantly, even in the same pedigree in which individuals shared the same causing mutation, they might present with totally different penetrance, expressivity, and symptoms.[25] However, in general, there are three common symptoms – movement disorder, psychiatric symptoms, and cognitive impairment, appearing in about 50–60% patients.[1] The relatively typical characteristics of *SLC20A2*-related IBGC in Chinese population including the pedigree in this study are early onset and paroxysmal

Table 2: *SLC20A2*-related IBGC of Chinese patients

Type of case	Onset (years)	Symptoms	Mutation	Region
Pedigree[6,7]	36	Headache, depression	c.1492G>A, p.Gly498Arg	6th exon
Pedigree[7]	1	Epilepsy, mental retardation, parkinsonism, ataxia	c.1802C>G, p.Ser601Trp	8th exon
Pedigree[7]	–	–	c.1802C>T, p.Ser601Leu	8th exon
Pedigree[8]	–	Depression	c.510delA, p.R172fsX19	2nd exon
Pedigree[9]	13	Repeat	c.185T>C, p.Leu62Pro	1st exon
Pedigree[9]	27	Dystonia	c.935-1G>A	Upstream of the 8th exon
Sporadic[9]	21	Involuntary movement	c.1470_1478delGCAGGTCCT p.Gln491_Leu493del	7th exon
Sporadic[9]	–	Headache	c.82G>A, p.Asp28Asn	1st exon
Pedigree[5]	12	Paroxysmal movement disorder	c.1086delC	8th exon
Pedigree of this report	49	Paroxysmal movement disorder, cognitive impairment	c.284C>T, p.Thr83Met	1st exon

IBGC: Idiopathic basal ganglia calcification; *SLC20A2*: Solute carrier family 20 member 2.

Table 3: *PDGEB*-related IBGC of Chinese patients

Type of case	Onset (years)	Symptom	Mutation	Region
Pedigree[12]	12	Paroxysmal movement disorder	c.232C>T, p.Arg78Cys	2nd exon
Sporadic[12]	33	Dazzle	c.220G>T, p.Glu74*	2nd exon
Sporadic[13]	30	Headache	c.232C>T, p.Arg78Cys	3rd exon

p.Glu74*: 220G>Tisa premature termination codon mutation causing premature transcription termination. IBGC: Idiopathic basal ganglia calcification; *PDGEB*: Platelet derived growth factor subunit B.

movement disorder.[5] Cognitive impairment in most patients is much milder compared with patients of other countries. Other symptoms are migraine and epilepsy.[5-8] Within pedigrees, radiological calcification might appear before clinical symptoms, but there was a positive relationship between severity of clinical symptoms and radiological calcification degree. While among pedigrees, there were huge differences in onset age, symptom severity, and types of symptoms. It has been reported about 40% mutation found within the 8th exon; the next is the 1st exon, accounting for about 30%, as it shown in Table 2. Hence, we could postulate that the 1st and the 8th exons might hot region of this disease.

PDGFB gene is the second common cause of single-gene IBGC,[10,11] and was first reported by Keller *et al*.[26] *PDGFB* gene plays a crucial role in the development of blood-brain barrier (BBB). Mutations causing loss of function of the gene results in disrupted BBB, which in turn leads to abnormality of metabolism of calcium and phosphate.[26,27] *PDGFB*-related cases are much more rare compared with *SLC20A2* ones. There are only two relevant reports.[12,13] The typical clinical symptoms are much milder than those carrying *SLC20A2* mutations, and movement disorder and atypical symptoms such as headache and slight memory decline are frequently observed. As for mutations in *PDGFB*, most mutations are located in the region of the 2nd exon covering a length of 220–230 bp, indicating that the 2nd exon was possibly a hot region for this disease. However, due to the paucity of reported cases, this speculation needs to be further confirmed in a larger cohort.

PDGFRB mutation is a newly discovered cause of IBGC and is relatively rare compared with the two above. The first case was not reported until 2013.[28] *PDGFRB* gene encodes for a subunit of platelet-derived growth factor receptor coupled with tyrosine kinase. Mutations in *PDGFRB* results in loss of function of the receptor, which places a detrimental impact on intracellular signaling transduction during the development of BBB and/or other processes, ultimately leading to disturbance of calcium and phosphate metabolism.[29] There were only 2 *PDGFRB*-positive cases in a screen among Chinese patients of non-*SLC20A2* and non-*PDGFB*, which implied that *PDGFRB* mutation was not common in Chinese patients with IBGC.[14]

To sum up, mutations in *SLC20A2* gene are the most common cause of IBGC in China, and the hot region for mutations are 1st and 8th exons. The second common cause is *PDGFB*, which has a mutational hot spot covering a length of 220–230 bp on the 2nd exon. Based on clinical manifestation among these patients, we concluded that Chinese IBGC patients with mutations mentioned above feature early onset and predominant paroxysmal movement disorder. Cognitive impairment is much milder. Moreover, other atypical symptoms such as headache and depression are frequently seen. Even so, there are significant differences from the range of severity to clinical manifestations both within and among pedigrees. In addition, *SLC20A2*-related IBGC accounts for about 40–50% among all these patients based on literature. *PDGFB* only explains a small proportion about 10%.[11] While a study of genetic screen among Chinese IBGC patients, without *SLC20A2* or *PDGFB* showed merely 1.4% positive rate of all these IBGC patients.[14] So what about those negative patients? How many genes related to IBGC are unknown? And what is the exact pathology

behind these reported mutations? If there could been curable method for these patients. All these questions need to be further explored either clinically or genetically. The clearer our understanding of the pathological courses is, the more likely a cure would be found.

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Conflicts of interest

There are no conflicts of interest.

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SLC20A2基因突变相关家族性特发性基底节钙化新位点报道及中国患者不同基因型导致的特发性基底节钙化临床特点分析

摘要

背景：特发性基底节钙化是以双侧基底节钙化和神经系统退行性病变为特征的遗传相关性疾病。本文我们报道了一个SLC20A2相关家族性特发性基底节钙化的新发位点，回顾并总结已经报道的上述各个基因型相关中国患者特发性基底节钙化的临床特点。

方法：首先，全面收集本家系先证者和家系成员的临床资料，包括病史、实验室检查和诊断相关的影像学资料。在取得相关人员知情同意的前体现，收集先证者和其父亲的外周血标本，并进行特发性基底节钙化相关基因的筛查。基因突变结果在家系内经一代测序验证，与表型共分离，并通过Polyphen-2软件预测极有可能为致病突变。其次，检索已经报道的中国特发性基底节病变的相关报道，总结不同基因型特发性基底节钙化的临床特点。

结果：通过基因测序、家系内验证和蛋白功能预测，我们发现一个导致特发性基底节钙化的SLC20A2基因新位点。通过分析总结文献，我们发现SLC20A2突变是中国单基因特特发性基底节钙化最常见的原因，其突变热点位于第一和第八号外显子区域。其次是PDGFB基因，

其突变热点位于二号外显子上长度为220-230bp的特定区域。此外，中国特发性基底节钙化的患者多表现为发病年龄早、运动症状较重、认知损害较轻。

结论：中国特发性基底节钙化患者表型和基因型均存在异质性，但也存在一定共性。在遗传突变基础上进一步机制研究能够帮助我能更清晰的了解疾病的发病机制，从而为不同基因型患者提供个体化治疗。