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Short communication

Clinical findings of autosomal-dominant striatal degeneration and *PDE8B* mutation screening in parkinsonism and related disorders

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ABSTRACT

Background: Autosomal-dominant striatal degeneration (ADSD) is a rare neurodegenerative movement disorder caused by mutations in the Phosphodiesterase 8B (*PDE8B*) gene.
Objective: To summarize the clinical and imaging features of a Chinese ADSD family and determine whether mutations in *PDE8B* are associated with Parkinson's disease (PD) or Parkinsonism.
Methods: Clinical, imaging and genetic findings in a Chinese ADSD family are reported. Rare, potentially pathogenic variants in *PDE8B* were searched in whole-exome sequencing datasets from 1714 PD or parkinsonism patients and 1039 controls.
Results: An ADSD diagnosis was confirmed by a nonsense mutation in *PDE8B* (p.E102X) in a patient and a presymptomatic carrier. Clinically, the patient exhibited progressive parkinsonism without tremor and ataxia phenotype. Neuroimaging showed an inhomogeneous increased signal in the patient's striatum on T1-weighted images but a decreased signal in the presymptomatic carrier. Diffusion tensor imaging (DTI) showed a disturbance in the white matter fiber distribution, especially between the lentiform nucleus and caudate nucleus, which was more prominent in the patient than in the presymptomatic carrier. Within the 1714 patients, three *PDE8B* missense variants were identified that were unlikely to be the cause of the parkinsonism phenotype according to the functional prediction and mutation types reported in ADSD.
Conclusions: For the first time, we described the typical ataxia phenotype in ADSD. A loss of white matter fiber integrity was shown on DTI scanning. No causative *PDE8B* mutation was discovered in our cohort of PD or Parkinsonism patients.

1. Introduction

Autosomal-dominant striatal degeneration (ADSD) is a rare monogenic disease caused by mutations in the phosphodiesterase 8B (*PDE8B*) gene [1], with the cardinal features of bradykinesia, muscle rigidity, and gait disturbance, resembling that of Parkinson's disease (PD), but lacking tremor, and is resistant to treatment with levodopa (L-DOPA) [1]. Neuroimaging demonstrates a characteristic signal change restricted to lesions in the striatum, including in the putamen, caudate nucleus and nucleus accumbens. Initially, a frameshift mutation [c.94G > C + c.95delT (p.V32Rfs*33)] in the phosphodiesterase 8B gene (*PDE8B*) was reported as the cause of ADSD in a large German family [2]. Subsequently, two other mutations, c.304G > T (p.E102X) and c.79delC (p.R27Afs*38), were reported in Japanese and Brazilian (of Portuguese ancestry) patients, respectively [3,4]. All three of these mutations result in the loss of all three functional domains of the PDE8B protein (Supplementary Fig. 1).

Recently, we performed whole-exome sequencing on a patient with clinical manifestations of slowly progressive parkinsonism and typical ataxia and discovered a nonsense mutation (NM_003719: c.304G > T, p. E102X) in the *PDE8B* gene, which is identical to the mutation discovered in Japan. Moreover, given the similar clinical features among ADSD, parkinsonism and related disorders, we searched for rare, potentially pathogenic variants in the *PDE8B* gene in a whole-exome

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sequencing datasets from 1714 patients with PD or parkinsonism without any pathogenic mutations in known PD genes and 1039 controls to determine whether variants in the *PDE8B* gene contribute to the parkinsonism phenotype.

2. Materials and methods

2.1. Subjects

An ADSD family and 1714 unrelated patients, consisting of 1411 PD patients and 303 parkinsonism patients, were of Han-Chinese descent and recruited from the outpatient neurology clinics of Xiangya Hospital, Central South University. Each PD patient was diagnosed with clinically established PD or clinically probable PD by at least two experienced neurologists according to movement disorder society (MDS) diagnostic criteria [5]. One thousand and thirty-nine geographically matched healthy controls were recruited at Xiangya hospital. The study was approved by the Ethics Committee of Xiangya Hospital, Central South University. Written informed consent was obtained from all subjects. All subjects in the video gave consent to be videoed for publication, including online publication and dissemination of the video material.

2.2. Clinical investigation

Detailed clinical data were obtained from the subjects in this study, and a clinical examination and evaluation were performed by at least two experienced neurologists. In the ADSD family, blood tests, including liver, kidney, glucose, lipid, ceruloplasmin, vitamin, thyroid, serum copper, and heavy metals tests, were performed. Computed tomography (CT), magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) scanning of the whole brain, awake electroencephalography (EEG), and neuropsychological and electrophysiological examinations were conducted on the proband (II:2) and the presymptomatic *PDE8B* gene mutation carrier (presymptomatic carrier III:1). The lumbar puncture was performed on the proband (Fig. 1).

2.3. Genetic testing

Genomic DNA was extracted from peripheral blood leukocytes using the phenol chloroform method. Whole-exome sequencing was performed in the proband, 1714 patients with PD or parkinsonism and 1039 controls as described previously [6]. Variants that fulfilled the following criteria were included for further analysis: (1) Variants with a minor allele frequency (MAF) ≤ 1% in the 1000 Genome Project (Phase 3) and the Genome Aggregation Database (genomAD r2.0.2); (2) Nonsynonymous, indels, and putative splice site variants; And (3) Pathogenicity, defined as being predicted as pathogenetic by at least five of 11 in silico tools according to the procedure described by Marialuisa Quadri [7] (Supplementary Table 1).

3. Results

3.1. Clinical features of the Chinese ADSD family

The proband was a 52-year-old woman who had slowly progressive bradykinesia for three years, accompanied by dysarthria, without signs of sensory deficits or limb weakness. Her mother also had bradykinesia and slurred speech but was never evaluated by a physician. The other family members were clinically unaffected. (with no neurological disorders).

Neurological examination of the proband showed mask-like face, slurred speech, decreased pharyngeal reflex, normal muscle strength in the four extremities, and a mildly increased muscle tone without tremor but with marked instability on retropulsion. The tendon reflex of the left lower extremity was slightly brisk but pyramidal signs were absent. She also had a wide-based gait, dysmetria, abnormal heel-knee-shin test, impaired finger-to-nose test and dysdiadochokinesia on both sides (Video 1). The scores of the Scale for Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS) were 10/40 and 19/100, respectively. The score of the Unified Parkinson's Disease Rating Scale (UPDRS) part III was 15/108.

Supplementary video related to this article can be found at doi:10.1016/j.parkreldis.2019.11.002

The results of the awake EEG, neuropsychological tests, and electrophysiological examinations were normal. The results of laboratory tests and CSF analysis were within normal limits. Levodopa was prescribed at a dose of 600 mg daily; however, no improvement was observed.

3.2. Imaging findings of the Chinese ADSD family

The head CT of the proband showed low density lesions in the putamen and caudate nucleus (Supplementary Fig. 2). The head MRI revealed a pattern of signal increase restricted to the bilateral basal ganglia on T2-weighted images and an inhomogeneous increased signal on T1-weighted images. The presymptomatic carrier (III:1, 31 years old) also showed an abnormal signal in the symmetric lesions of the striatum, but with some differences compared to her mother (Fig. 1C–G): first, the lesion area was more extensive in the proband than in the presymptomatic carrier. The bilateral thalamus, caudate nucleus, putamen and nucleus accumbens of the proband showed an increased signal on T2-weighted images, whereas only the bilateral caudate nucleus, putamen and nucleus accumbens showed an increased signal in the presymptomatic carrier. Next, T1-weighted images for the proband showed a heterogeneous mixture of increased and decreased signal in the caudate nucleus, putamen and nucleus accumbens, while only decreased signal in the affected areas was observed for the presymptomatic carrier. Moreover, DTI imaging exhibited decreased fractional anisotropy (FA) in the striatum, demonstrated a loss of white matter fiber integrity, especially between the lentiform nucleus and caudate nucleus, which was more so in the proband than in the presymptomatic carrier.

3.3. Genetic testing of the ADSD family and parkinsonism patients

Whole-exome sequencing of the proband uncovered a heterozygous mutation (c.304G > T, p. E102X) in the *PDE8B* gene, which was confirmed by Sanger sequencing. Cosegregation results showed that only the proband's daughter (III:1) carried this mutation, and since she had no symptoms, she was assumed to be a presymptomatic carrier (Fig. 1).

Among the 1714 patients with PD or parkinsonism, three heterozygous variants, c.203G > C:p.R68P, c.424C > T:p.R142C and c.2411C > T:p.A804V, were detected. All three variants were absent or extremely rare in the public database (≤0.002). No variant fulfilling the selection criteria was found in the 1039 healthy controls. According to in silico prediction, variants c.424C > T and c.203G > C were predicted to be likely benign, and c.2411C > T showed a likelihood of pathogenicity and was therefore included for further discussion (as detailed in Supplementary Table 1).

4. Discussion

We report herein an ADSD patient along with her presymptomatic carrier daughter, and describe the clinical and imaging features. To the best of our knowledge, only 3 ADSD families have been reported thus far (Table 1), and there have been no reports regarding DTI imaging findings in ADSD. In spite of the slowly progressive bradykinesia and dysarthria in the patient, we also detected a wide-based gait, dysmetria, abnormal heel-knee-shin test, impaired finger-to-nose test and dysdiadochokinesia on both sides, which is the first time that the typical

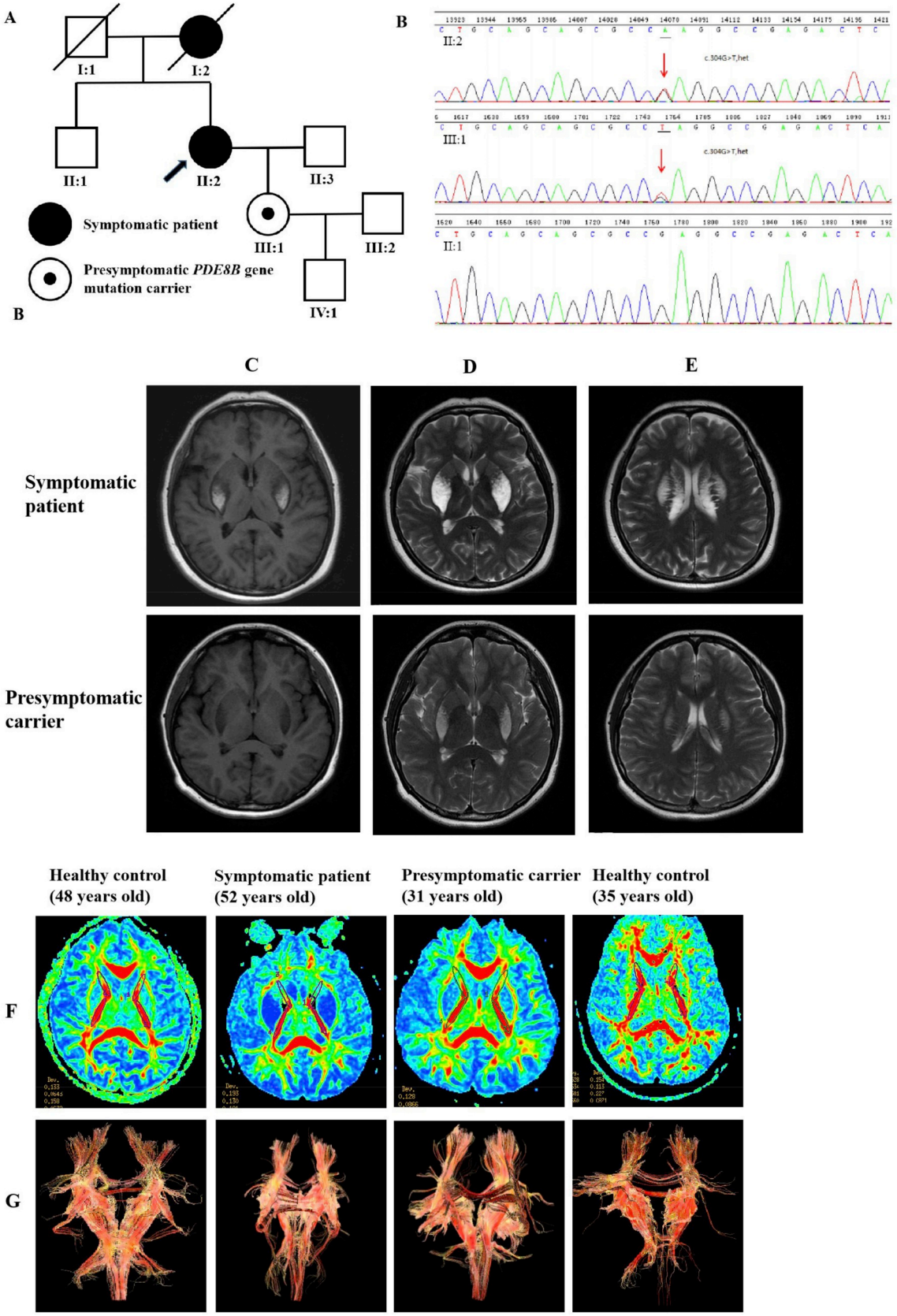

Fig. 1. Pedigree, genetic and imaging findings of the ADSD family. A: ADSD pedigree (arrow points to the proband II:2, square = male, circle = female, slashed symbol = deceased, filled symbol = affected, empty symbol = unaffected, circle with a point inside = presymptomatic *PDE8B* mutation carrier). B: Sanger sequencing of the *PDE8B* gene. The red arrow indicates the mutation site (c.304G > T). C-E: Neuroimaging results of the patient (above) and presymptomatic carrier (below). C: T1-weighted images. D and E: T2-weighted images. F-G: Diffusion tensor imaging, reduced fractional anisotropy in the striatum of the patient and presymptomatic carrier versus age-matched healthy controls).

Table 1
Review of ADSD patients with *PDE8B* mutations.

Study	Population	Mutations	Age at onset (years)	Dysarthria	Bradykinesia	Other Symptoms/signs	Muscle tone	Tremor	Tendon reflexes	Pyramidal signs	Thyroid function	Response to levodopa
Kuhlenbäumer G et al.	German	c.94G > C, c.95delT,p.V32Rfs*33	40–50	Y	Y	dysdiadochokinesia	↑	–	very brisk	–	–	–
Azuma R et al.	Japanese	c.304G > T, p. E102X	17,32	Y	Y	P1: Micrographia P2: mask-like face, monotonous speech	↑	–	NA	NA	NA	–
Barsottini OG et al.	Brazilian (of Portuguese ancestry)	c.79delC, p. R27Afs*38	60	Y	Y	NA	NA	NA	brisk	NA	NA	–
Current study	Chinese	c.304G > T, p.E102X	49	Y	Y	Mask-like face, ataxia	↑	–	slight brisk	–	–	–

Study	Imaging studies			
	MRI T1-weighted images signal change	MRI T2-weighted images signal change	CT	Other imaging findings
Kuhlenbäumer G et al.	Affected: central inhomogeneous increased signal (PU, CA, AC) Mildly affected: homogeneously decreased signal (PU, CA, AC)	Increased signal (PU, CA, AC)	Hypodense and sharply demarcated of the affected structures	Normal Proton MR spectroscopy
Azuma R et al.	Decreased signal (CA and PU).	Increased signal (CA, PU)	Symmetrical low-density (BG)	PET scans: markedly decreased uptake [11C]CFT, [11C]RAC and [18F]FDG (PU) Relatively preserved uptake [11C]CFT, [11C]RAC (CA)
Barsottini OG et al.	Decreased signal (PU, AC, CA, and the connection bundles between the PU and the CA)	Symmetric bilateral Increased signal in the affected areas	NA	DWI: bilateral symmetrical restricted diffusion (the dorsal portion of the posterior 2/3 of the PU, AC, tail of CA, and HI).
Current study	P: a heterogeneous mixture signal (CA, PU, AC). Presymptomatic carrier: decreased signal (CA, PU, CL, AC)	P: increased signal (TH, CA, PU, AC) Presymptomatic carrier: increased signal (CA, PU, CL, AC)	Low density lesions (PU,CA)	DTI: white matter fiber distribution disturbance (especially between LE and CA)

Y, yes; NA, not available; ↑, sightly increased; -, negative; P, patient.
CFT, [11C]2ß-carbomethoxy-3β- (4-fluorophenyl) tropane; RAC, raclopride; FDG, [18F] fluorodeoxyglucose.
DTI, Diffusion tensor imaging; DWI, Diffusion-weighted imaging.
CA, caudate nucleus; PU, putamen nucleus; CL, claustrum nucleus; AC, nucleus accumbens; HI, hippocampus; BG, the basal ganglia; TH, thalmus; LE, lentiform nucleus.

ataxia phenotype has been reported in ADSD.

In this study, the presymptomatic carrier also showed characteristic, symmetric MRI abnormalities of the basal ganglia. The greater lesion area in the patient compared to the presymptomatic carrier might present an opportunity to decipher the natural history of ADSD and explain the difference in their clinical manifestations; otherwise, the damage to the bilateral basal ganglia might not be the only contributing factor to the disease severity. We found a heterogeneous mixture signal (increased and decreased) on the T1-weighted images of the patient's striatum, while in the presymptomatic carrier, the images only showed a decreased signal. Therefore, we hypothesize that the increased signal on the T1-weighted images might be a biomarker of pathological damage which is consistent with the severity of the clinical manifestation. The abnormal signal might be caused by bleeding, calcification, lipid deposition, or accumulation of paramagnetic substances. The CT scan of the patient essentially rules out the possibility of bleeding and calcification; the difference between the fat signal of the scalp and the bilateral basal ganglia signal intensity makes lipid deposition unlikely. Therefore, we are more inclined to believe the speculative conclusion reported by Kuhlenbäumer G that the accumulation of paramagnetic substances led to the increased signal on T1-weighted images [1,8,9]. However, whether accumulation causes neurodegeneration or degeneration causes accumulation still needs to be elucidated. The increased signal on T2-weighted images, which was restricted to the caudate nucleus, putamen and nucleus accumbens, is consistent with previous reports [3].

No obvious abnormal signal of white matter fibers in the internal capsule was found on T2-weighted images. Unexpectedly, the DTI images showed a loss of white matter fiber integrity and even more so in the patient than in the presymptomatic, especially between the lenticular nucleus and caudate nucleus. Azuma et al. [3]suggested that a defect in signaling through dopamine receptors might cause ADSD. Interestingly, our results suggest that the striatal conduction bundle might also play an important role in the pathogenesis of ADSD.

Due to the similar clinical features among ADSD, parkinsonism and related disorders, we searched for rare, potentially pathogenic variants in the *PDE8B* gene in whole-exome sequencing datasets from 1714 patients with PD or parkinsonism and 1039 controls. We found three rare missense variants (c.203G > C:p.R68P, c.424C > T:p.R142C and c.2411C > T:p.A804V) in patients, which were absent in controls. According to in silico prediction, variant c.2411C > T showed a likelihood of pathogenicity. However, we cannot conclude that the variant contributes to the parkinsonism phenotype. Six transcript variants encoding different isoforms have been found for *PDE8B*, the longest one (*PDE8B1*) encoding a protein of 885 amino acids, which includes three domains: REC (cheY-homologous receiver), PAS (Per, Arnt, and Sim) and a C-terminal catalytic PDE domain [10]. According to previous reports, the mutations in ADSD patients were all truncating mutations and resulted in the loss of all three functional domains of the PDE8B protein, which might lead to a complete loss of function of the truncated protein (Supplementary Fig. 1). The variants found in our cohort of 1714 patients, on the other hand, were all missense variants. Therefore, there is a reason to assume that the variants reported here may not be enough to be the contributing factor to the parkinsonism phenotype. However, further functional studies are needed to confirm the pathogenicity of the variants.

In conclusion, our study broadened the clinical and pathogenetic spectrum of ADSD, and no causative *PDE8B* mutation was discovered in parkinsonism and related disorders.

Author contributions

Jie Ni performed research, analyzed the data, and wrote the paper. Xiaoping Yi conducted the neuroimaging analysis. Zhen Liu performed WES analysis. Weining Sun and Yanchun Yuan summarized the clinical data of patients. Jie Yang, Hong Jiang, Lu Shen, Beisha Tang and Yunhai Liu supervised the study. Junling Wang directed the overall research and wrote the manuscript.

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Declaration of competing interest

All authors report that they have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.11.002.

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