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CASE REPORT

Novel compound heterozygous *GPR56* gene mutation in a twin with lissencephaly: A case report

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Abstract

BACKGROUND

Lissencephaly (LIS) is a malformation of cortical development with broad gyri, shallow sulci and thickened cortex characterized by developmental delays and seizures. Currently, 20 genes have been implicated in LIS. However, *GRP56*-related LIS has never been reported. *GRP56* is considered one of the causative genes for bilateral frontoparietal polymicrogyria. Here, we report a twin infant with LIS and review the relevant literature. The twins both carried the novel compound heterozygous *GPR56* mutations.

CASE SUMMARY

A 5-mo-old female infant was hospitalized due to repeated convulsions for 1 d. The patient had a flat head deformity that manifested as developmental delays and a sudden onset of generalized tonic-clonic seizures at 5 mo without any causes. The electroencephalography was normal. Brain magnetic resonance imaging revealed a simple brain structure with widened and thickened gyri and shallow sulci. The white matter of the brain was significantly reduced. Patchy long T1 and T2 signals could be seen around the ventricles, which were expanded, and the extracerebral space was widened. Genetic testing confirmed that the patient carried the *GPR56* gene compound heterozygous mutations c.228delC (p.F76fs) and c.1820_1821delAT (p.H607fs). The unaffected father carried a heterozygous c.1820_1821delAT mutation, and the unaffected mother carried a heterozygous c.228delC mutation. The twin sister carried the same mutations as the proband. The patient was diagnosed with LIS.

CONCLUSION

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This is the first case report of LIS that is likely caused by mutations of the *GPR56* gene.

Key Words: Lissencephaly; Epilepsy; *GPR56* mutations; Compound heterozygous mutations; Case report

Core Tip: We report a twin infant with lissencephaly (LIS). The twins both carried the novel compound heterozygous *GPR56* mutations, p.F76fs and p.H607fs, which have not been reported in the Human Gene Mutation Database. To our knowledge, this is the first case of *GRP56*-related LIS. Therefore, *GPR56* gene mutations may lead to LIS.

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INTRODUCTION

Lissencephaly (LIS) is a group of abnormal cerebral cortical dysplasias caused by the defective migration of neurons. It can be diagnosed clinically by neuroimaging. It is characterized by thickening of the cerebral cortex, widening of the gyri, and disappearance or shallowness of the sulci. The complete disappearance of the sulci and gyri showing smooth surface of the brain is called agyria and is seen in severe cases [1]. According to the neuroimaging, LIS is divided into six grades, ranging from severe agyria (grade 1) to mild subcortical band heterotopias (grade 6). The severity of nerve damage is closely related to the grade of LIS and cortical thickening, and the mortality rate of severe LIS is high[2]. In the early stages, patients often exhibit developmental delays and hypotonia, followed by seizures, and a severe intellectual disability eventually. Although a LIS patient may develop normally in the neonatal period, many neonates suffer from persistent feeding problems and different types of epilepsy, which are difficult to cure[3]. An individual with mild LIS and normal intelligence has been reported[4]. Currently, 20 genes have been implicated in LIS. Many of these genes are microtubule genes[5,6].

GPR56 (OMIM#606854, NM_0001145773) encodes an orphan G protein-coupled receptor (GPCR) that is extensively expressed in the nervous system and is essential for the normal development of the cerebral cortex and cerebellar morphology[7-9]. The reported mutations of the *GPR56* gene have been confirmed to be related to bilateral frontoparietal polymicrogyria (BFPP)[10].

Herein, we report a twin infant with LIS who came from a nonconsanguineous family. The twins both carried a novel compound heterozygous *GPR56* mutation. To our knowledge, this is the first case of *GRP56*-related LIS.

CASE PRESENTATION

Chief complaints

A 5-mo-old female infant was hospitalized due to repeated convulsions for 1 d.

History of present illness

The patient was admitted to the Children's Hospital of Nanjing Medical University due to repeated convulsions. The patient had a sudden onset of generalized tonic-clonic seizures without any causes. In addition, she had a flat head deformity and developmental delays.

History of past illness

The patient had no history of past illness.

Personal and family history

The patient was the first child of nonconsanguineous Chinese parents. She was delivered by cesarean section due to twin pregnancy at 32 wk of gestation, with a birth weight of 2.6 kg. No intrauterine distress or postnatal asphyxia had occurred. She had a twin sister with LIS.

Physical examination

The patient showed a flat head deformity. The neurological examination was normal. There were no other abnormal signs.

Laboratory examinations

The electroencephalography and laboratory findings (full blood count, liver, kidney and thyroid function tests, creatine kinase, uric acid, metabolic study and chromosome karyotyping) were normal.

Imaging examinations

Brain magnetic resonance imaging (MRI) revealed a simple brain structure, with widened and thickened gyri and shallow sulci. The white matter of the brain was significantly reduced. The patchy long T1 and long T2 signals could be seen around the ventricles, which were expanded, and the extracerebral space was widened (Figure 1).

FINAL DIAGNOSIS

According to the clinical characteristics, imaging and genetic test findings (Figure 2), the infant was diagnosed with LIS.

TREATMENT

During the hospital stay, the patient had no epileptic seizures. She received rehabilitation, but anti-epileptic treatment was refused.

OUTCOME AND FOLLOW-UP

The patient experienced repeated convulsions after she was discharged from hospital. The convulsions occurred once a day to more than ten times a day without any causes, each episode lasting several minutes. She died 3 mo later.

DISCUSSION

The *GPR56* gene spans 45 kb and consists of 14 exons encoding an orphan GPCR of 693 amino acids[7,11]. GPR56 is a member of the adhesion GPCR family, which has an N- and a C-terminal fragment and a GPCR proteolytic site[12]. In the central nervous system, GPR56 plays an important role in the normal development of the cerebral cortex and cerebellar morphogenesis[8]. In the peripheral nervous system, GPR56 can regulate the formation and maintenance of myelin sheaths[13]. Therefore, the normal expression of GPR56 is essential for the function of the nervous system.

It is known that mutations of the *GPR56* gene are related to BFPP (Table 1). The clinical manifestations of BFPP are overall growth retardation and seizures. MRI shows symmetrical polygyria (the frontal parietal area is the most serious part), ventricular enlargement, and bilateral white matter changes. Twenty-eight pathogenic *GPR56* mutations related to the BFPP phenotype have been reported[11,14]. The affected individuals inherit the mutants in an autosomal recessive mode. The majority of missense mutations resulted in similar clinical symptoms, indicating that the similar phenotype might be caused by the same mechanism. However, the mechanism remains unclear, although it may involve GPR56 trafficking and a decrease in receptor

Table 1 Summary of *GPR56* mutations

Ref.	Mutation	Exon/intron	Case number	Ethnicity	Consanguinity	Motor delay	Cognitive delay	Seizure	MRI		
									Gyri	White matter abnormalities	Brainstem/cerebellum
Piao *et al*[10, 11], 2004 and 2005	c.112C>T (p.R38W)	Exon 3	2	Arabic (Qatar)	First cousin	+	Moderate	GTC, myoclonic	BFPP	Patchy signal change	Small brainstem
						+	NA	+			
			1	Arabic (UAE)	First cousin	+	+	NA	BFPP	Reduced volume, patchy signal change	Slightly small pons and vermis
	c.113G>A (p.R38Q)	Exon 3	1	Turkish	First cousin	+	+	+	BFPP	Severely reduced volume, patchy signal change	Small pons and vermis
	c.263A>G (p.Y88C)	Exon 3	2	French Canadian	N	+	+	NA	BFPP	Reduced volume, patchy signal change	Small pons, small/dysplastic cerebellum
	c.739-746 delCAGGACC (p.Q246Tfx*72)	Exon 5	2	Indian	N	+	+	Blank episodes	BFPP	Reduced volume, patchy signal change	Slightly small pons and vermis
						+	+	AS			
			1	Pakistani	First cousin	Severe	Severe	Generalized	BFPP	Patchy radiolucency	Small cerebellum
			1	Afghani	First cousin	Moderate	+	NA	BFPP	Reduced volume, patchy signal change	Small pons and superior vermis
	c.E5- 1G>C (NA)	Exon 5	2	Palestinian	N	+	+	Episodes of startles	BFPP	Reduced volume, periventricular signal change	Small pons and superior vermis
	c.1036T>A(p.C346S)	Exon 8	2	Palestinian	First cousin	+	+	NA	BFPP	Reduced volume, patchy signal change	Small pons and cerebellum
			1	Palestinian	First cousin	+	Severe	+	BFPP	Reduced volume, frontal subcortical signal change	Small brainstem and cerebellum
	c.1046G>C(p.W349S)	Exon 8	2	Israeli Jewish	First cousin	+	+	GTC	BFPP	Reduced volume, patchy signal change	Small pons and vermis
						+	+	Myoclonic	BFPP		
			1	Israeli Jewish	N	+	Severe	+	BFPP	Patchy signal change	Small vermis
	c.IVS9+3G>C (NA)	Intron 9	3	Palestinian	First cousin	+	+	FS, atonic-drop	BFPP	Patchy signal change	Slightly small pons and superior vermis
						+	Moderate	GTC, AS	BFPP		
						Severe	Severe	FS, GTC	BFPP		

			2	Palestinian	First cousin	+	Severe	GTC, atonic	BFPP	Patchy signal change	Small pons and superior vermis
						+	Severe	No	BFPP		
	c.1693C>T (p.R565W)	Exon 13	3	Arabic (Bedouin)	C	+	Severe	GTC, myoclonic	BFPP	Reduced volume, patchy signal change	Small vermis
			1	Italian	Second cousin	+	+	+	BFPP	Reduced volume, patchy signal change	Slightly small vermis
	c.1919T>G (p.L640R)	Exon 13	1	Hispanic	N	+	+	+	BFPP	Mildly reduced volume, patchy signal change	Slightly small cerebellar hemispheres
Parrini *et al* [18], 2009	c.97C>G (p.R33P)	Exon 2	2	Turkish	C	+	Severe	Atypical absences, GTC, tonic	BFPP	NA	NA
						+	Severe	Tonic, atypical absences, recurrent nonconvulsive status epilepticus	BFPP	Patchy signal change	NA
	c.235C>T (R79X)	Exon 2	1	Italian	C	+	Severe	Infantile spasms, tonic and atonic seizures	BFPP	Patchy signal change	NA
	c.1693C>T (p.R565W)	Exon 13	1	Italian	C	+	Severe	Tonic atonic GTC, atypical absences, recurrent nonconvulsive statusepilepticus	BFPP	Patchy signal change	Slightly small vermis
Bahi-Buisson *et al* [19], 2010	c.174-175insC (p.E59Rfs*24)	Exon 3	2	NA	C	NA	Severe	+	NA	NA	NA
						Walking at 4 yr	Severe	Focal seizures	BFPP	Patchy periventricular predominance	Hypoplastic pons
	c.272G>A (p.C91Y)	Exon 3	2	NA	C	Walking at 2 yr	Severe	NA	BFPP	Patchy	Hypoplastic pons
						Walking at 2 yr	Severe	GTC/atypical absence, atonic seizures	BFPP	Patchy periventricular and frontal predominance	Hypoplastic pons, Cyst in the ventral pons
	c.367C>T (p.Q123X)	Exon 3	1	NA	C	+	Severe	Focal seizures, GTC	BFPP	Patchy periventricular and frontal predominance	Hypoplastic pons, Cyst in the ventral pons
	c.671delA (p.D224Wfs*96)	Exon 5	3	NA	C	Walking at 4 yr	Severe	GTC	BFPP	Patchy periventricular and frontal predominance	Hypoplastic pons
						Walking at 18 mo	Severe	GTC	BFPP		

						Sitting without support	Severe	GTC	BFPP	Diffuse	Hypoplastic pons
	c.1215-1216delC (p.L406S406fs*41)	Exon 10	1	NA	C	Walking acquired but subsequently lost (11 yr)	Severe	+	BFPP	Patchy	Hypoplastic pons
	c.1254C>G (p.C418W)	Exon 10	3	Pakistani	First cousin	Walking at 5 yr	Severe	GTC	BFPP	Diffuse	Hypoplastic pons
						Walking at 5 yr	Severe	GTC	BFPP	Patchy with subcortical and frontal predominance, reduced volume	Severely hypoplastic pons with posterior concavity, cyst in the ventral pons
						NA	NA	NA	NA	NA	NA
	c.1345delCTG (p.L449del)	Exon 11	1	NA	C	Walking at 3 yr	Severe	Atypical absence	BFPP	Patchy with subcortical predominance	Severely hypoplastic pons with posterior concavity
	c.1453C>T (p.S485P)	Exon 11	2	NA	C	Walking at 18 mo	Severe	Focal seizures, generalized tonic seizures	BFPP	Patchy with subcortical and frontal predominance	Hypoplastic pons
						Walking at 18 mo	Severe	Focal seizures	BFPP		
Luo *et al* [20], 2011	c.1486G>A (p.E496K)	NA	1	Yemeni	First cousin	Walking	Severe	Tonic-clonic seizures	BFPP	Asymmetric areas of abnormal signal in the white matter of both cerebral hemispheres	Mild hypoplasia of the inferior cerebellar vermis and pons
Quattrocchi *et al*[16], 2013	c.105C>A (p.C35X)	Exon 2	1	NA	NA	Ataxic gait	Severe	Focal seizures, myoclonic	BFPP	Patchy subcortical and periventricular white matter abnormalities	Mildly hypoplastic cerebellar vermis, flattening of the ventral aspect of the pons, hemispheric cerebellar cysts, vermian cysts
	c.429G>A (p.W143X)	Exon 2	1	NA	NA	Ataxic gait	Moderate	No	BFPP	Patchy subcortical and periventricular white matter abnormalities	Mildly hypoplastic cerebellar vermis, flattening of the ventral aspect of the pons, hemispheric cerebellar cysts, vermian cysts
	c.1453C>T (p.S485P)	Exon 11	2	NA	NA	Walking at 18 mo	Severe	GTS, focal seizures	BFPP	Patchy subcortical and periventricular white matter abnormalities	Hypoplastic pons and superior vermis, hemispheric cerebellar cysts, vermian cysts

						Walking at 22 mo	Severe	Focal seizures	BFPP	Patchy subcortical and periventricular white matter abnormalities	Hypoplastic pons and superior vermis, hemispheric cerebellar cysts, vermian cysts
	c.1796-1801delTGCGCC/insAGATCCTGTGGGCAGAT (premature stop codon at position 614)	Exon 12	1	NA	NA	Ataxic gait	Moderate	No	BFPP	Patchy subcortical and periventricular white matter abnormalities	Flattening of the ventral aspect of the pons, hemispheric cerebellar cysts
Fujii *et al* [21], 2014	c.107G>A and c.113G>A(p.S36N and p.R38Q)	Exon 2	1	Japanese	N	Able to walk with help	Severe	Complex partial seizures, tonic seizures, epileptic spasms	BFPP	Patchy high signals in the frontal subcortical	Hypoplastic pons
Desai *et al* [22], 2015	c.113G>A (p.R38Q)	Exon 3	1	Indian (Marathi)	C	Mode-rate	Moderate	Complex febrile seizures	BFPP	Diffuse	Mild thinning and cerebellar cysts
	c.739–746 delCAGGACC (p.Q246Tfx*72)	Exon 4	1	Indian (Punjabi)	N	Severe	Mild	No	BFPP	Frontal and periventricular	Mild thinning and cerebellar cysts
	c.739–746 delCAGGACC (p.Q246Tfx*72)	Exon 4	1	Indian (Sindhi)	N	Severe	Moderate	No	BFPP	Frontal and periventricular	Inferior vermian hypoplasia; cerebellar cyst
	c.1426 C>T (p.R476X)	Exon 12	1	Indian (Gujarati)	C	Severe	Severe	Generalized seizures	BFPP	Diffuse	Mild thinning and cerebellar cysts
Santos-Silva *et al*[17], 2015	811C > T (R271X)	Exon 6	1	Caucasian	N	Severe	Severe	Hot water epilepsy	BFPP	Reduced volume, patchy signal change	Hypoplasia of the pons and cerebellar vermis
Öncü-Öner *et al*[14], 2018	811C > T (R271X)	Exon 6	1	NA	C	Severe	Severe	Focal onset bilateral tonic-clonic seizure	BFPP	Yes	Thin brainstem and normal cerebellar structure
Current report	c.228delC and c.1820-1821del AT (p.F76fs and p.H607fs)	Exon 6 and Exon 13	2	Chinese	N	+	Severe	GTC	LIS	Reduced volume, patchy signal change	Normal
						+	+	No	LIS	NA	NA

AS: Absence of seizure; BFPP: Bilateral frontoparietal polymicrogyria; C: Consanguineous; FS: Febrile seizure; GTC: General tonic-clonic seizures; LIS: Lissencephaly; MRI: Magnetic resonance imaging; N: Nonconsanguineous; NA: Not available; UAE: United Arab Emirates.

levels at the cell membrane[15-17]. GPR56 knockdown did not affect the migration of neural progenitor cells, while GPR56 overexpression inhibited the migration of neural progenitor cells. This mechanism might occur through the reorganization of cerebral cortex actin to change the cell morphology and regulate neural progenitor cell behavior[8]. LIS is caused by premature stop of neuronal migration, which might explain the mechanism of the *GPR56* mutations causing LIS in the present case.

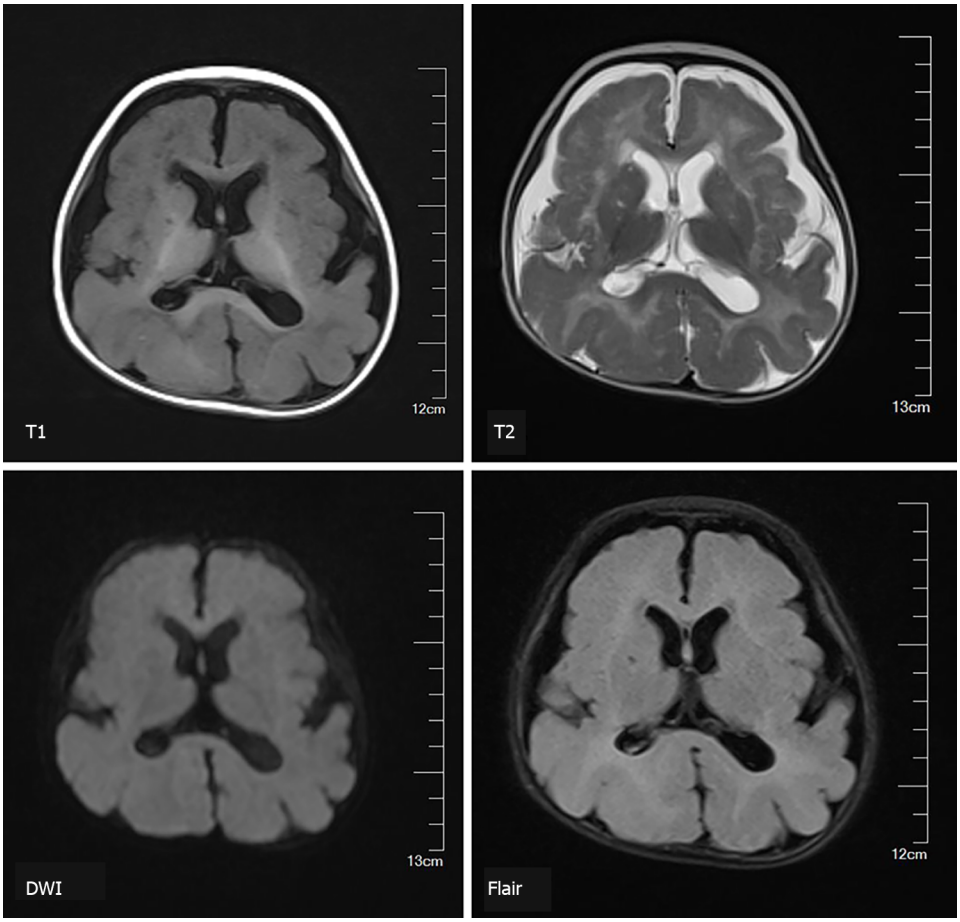

Figure 1 Brain magnetic resonance imaging of the proband revealed a simple brain structure, with widened and thickened gyri and shallow sulci.

The development of the brain is a delicate and complex physiological process, and the proper migration of neurons is one of the most critical steps. LIS is brain dysplasia caused by the premature stop of neuronal migration. Type I LIS is characterized by a thickened cerebral cortex (10-20 mm, whereas normal is 4 mm), but no other brain development malformations, such as severe congenital microcephaly, corpus callosum hypoplasia, or cerebellar hypoplasia[2]. Microscopically, the cerebral cortex in LIS is divided into four thick and dysplastic layers: The molecular layer, the superficial cellular layer, the cell spare layer, and the deeper cellular layer; the normal cerebral cortex has six layers[1].

Currently, 20 genes have been reported to be associated with LIS, and many of them are microtubule genes[5,6]. In a cohort study of 811 patients with LIS, the overall mutation frequency of the entire cohort was 81%, of which *LIS1* accounted for 40%, followed by *DCX* (23%), *TUBA1A* (5%), and *DYNC1H1* (3%). Other genes accounted for 1% or less. Interestingly, the cause of LIS in 19% of the patients was unknown, which indicates that additional genes are involved and need to be discovered[6]. There have been no other reports of LIS caused by *GPR56* gene mutations. Therefore, the relationship between LIS and *GPR56* still needs further research.

There is no specific treatment method for LIS. Current treatments typically involve symptomatic relief, such as anti-epileptic treatment and rehabilitation training. Studies in animal models have shown that it might be possible to restart neuronal migration by re-expressing the missing/nonfunctional genes after birth[2]. Even if the degree of cortical deformity is partially improved, it may significantly decrease seizure frequency and clinical severity[2]. Therefore, with the advances in genetic testing and medical technology, the diagnosis and treatment of LIS will continue to be improved and optimized.

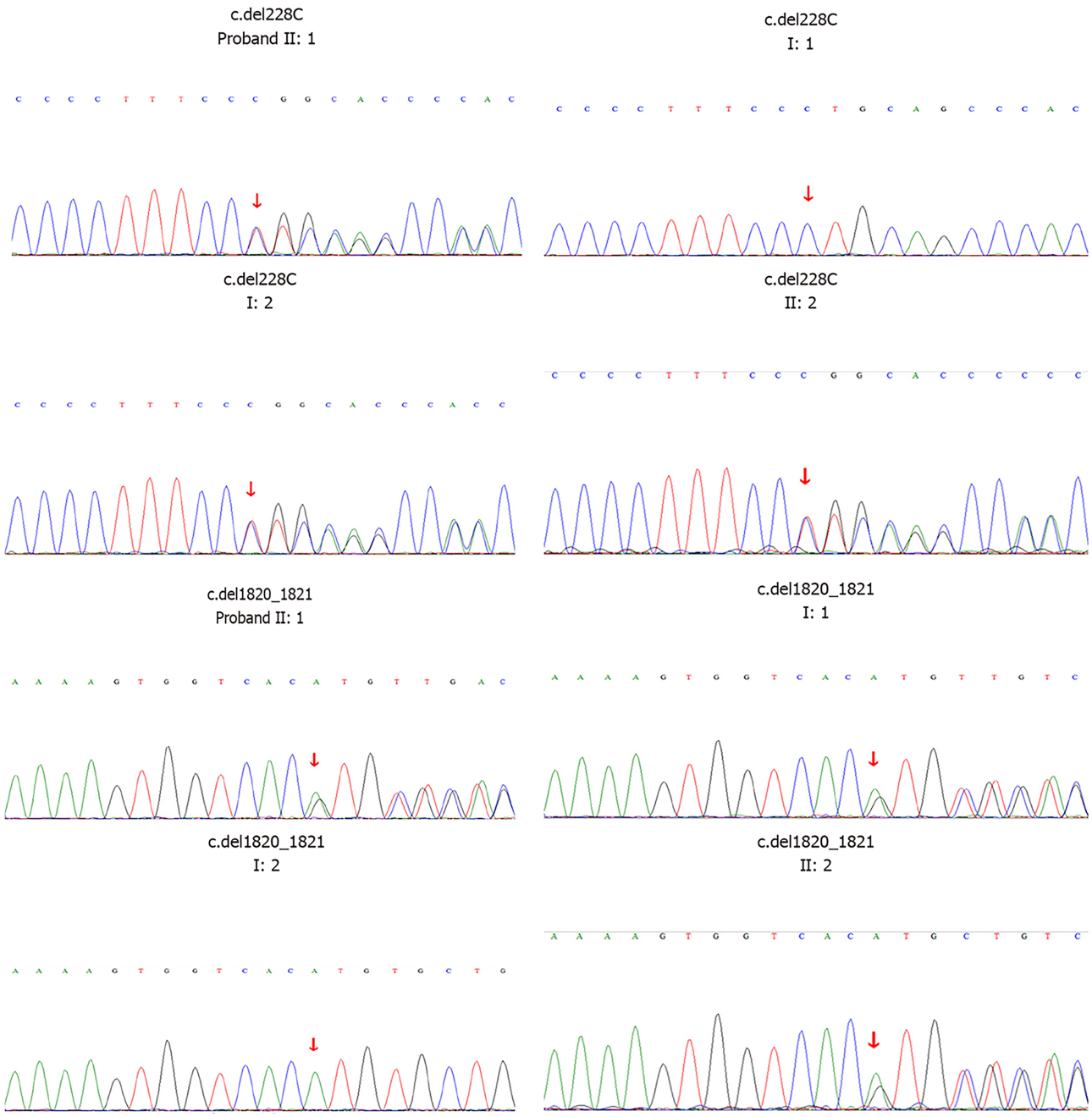

Figure 2 Sanger sequencing of the proband and her family members.

CONCLUSION

The compound mutations in the *GPR56* gene identified in the twin sisters with LIS were novel and unreported mutations. This finding has broadened our knowledge of the clinical manifestations of LIS and increased our understanding of *GPR56*. Genetic testing is necessary when patients suffer from LIS symptoms.

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