

Familial moyamoya disease in two Turkish siblings with same polymorphism in RNF213 gene but different clinical features

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Abstract

Background Moyamoya disease is an uncommon, progressive, and occlusive cerebrovascular disorder, predominantly affecting the terminal segment of the internal carotid arteries and its main branches. This occlusion results at the formation of a compensatory collateral arterial network (moyamoya vessels) developing at the base of the brain. The c.14576G>A

variant in ring finger protein 213 (RNF213) was recently reported as a susceptibility gene for moyamoya disease.

Methods We describe two Turkish pediatric siblings with moyamoya disease born to consanguineous, unaffected Turkish parents.

Results The first patient (proband) is a 2-year-old boy who presented with afebrile focal seizures, moderate psychomotor retardation, paresis in the left upper and lower extremity, multiple infarctions of the brain, stenosis of the bilateral internal carotid artery and the middle cerebral artery, and stenosis of the right posterior cerebral artery. The second patient is a 10-year-old girl who is an elder sister of proband. She showed normal psychomotor development, millimetric signal enhancement without diffusion limitation of the brain, and stenosis of the bilateral internal carotid artery.

Conclusion We herein report pediatric sibling patients of moyamoya disease who have homozygous wild-type c.14576G>A variant in RNF213, showing different clinical course and disease severity. This is the first report of pediatric siblings with moyamoya disease from Turkey validating the genetic background of most frequent variant in East Asian patients with moyamoya disease.

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Keywords Cerebrovascular disease · Moyamoya disease · RNF213 gene · Sibling patients · Child

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Abbreviations

ANCA	Antineutrophil cytoplasmic antibody
ANA	Antinuclear antibody
MMD	Moyamoya disease
ICA	Internal carotid arteries
MCA	Middle cerebral artery
PCA	Posterior cerebral artery
RNF	Ring finger protein

MRA	Cerebral magnetic resonance angiography
MRI	Magnetic resonance imaging
EEG	Electroencephalogram

Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disease that is characterized by progressive occlusion of the supraclinoid segment of the bilateral internal carotid arteries (ICA) and its main branches, associated with the development of dilated, fragile, compensatory vascular network at the base of the brain [4]. Although the incidence of MMD is not very high, it is an important cause of pediatric cerebrovascular stroke [1, 11, 12]. Prompt diagnosis and management are crucial in improving irreversible and devastating neurological deficits and intellectual impairments. MMD indicates wide regional variation, such that it is more prevalent in Far Eastern countries, especially in Japan and South Korea, than in Europe and the Americas [12].

Etiology

Although the etiology of MMD is still unknown, genetic factors have been strongly suggested due to the high incidence of familial occurrence. The ring finger protein 213 (RNF213) gene was identified as an important susceptibility gene of MMD in the recent genetic studies among East Asian population [3]. The c.14576G>A variant in exon 61 of RNF213 (rs112735431) was identified in 95 % of familial patients with MMD with an odds ratio of 259. Furthermore, patients having this variant were found to correlate with significantly earlier disease onset and a more severe form of MMD [7]. In addition, the homozygous c.14576G>A genotype exhibits a more severe type of MMD with a poor prognosis when compared with heterozygotes [7, 8].

Diagnostic imaging

The diagnosis of MMD is made based on characteristic radiographic appearances including narrowing of the terminal segments of the ICAs. Radiographic suspicion of MMD typically begins with either a magnetic resonance imaging (MRI) study or computerized tomography of the brain. Cerebral angiography remains the gold standard for the diagnosis of MMD [4, 12].

Clinical presentation

Clinical manifestations of this syndrome in children include recurrent ischemic attacks, multiple cerebral infarctions, seizures, headache, and developmental delay [1, 4, 12].

In the present study, we describe two pediatric siblings with MMD born to consanguineous, unaffected Turkish parents. Although both of them have carried the same genetic background, wild-type G/G in c.14576G>A genotype, they present different clinical course and disease severity.

Case presentation

Case 1

Case 1 (proband) is a 2-year-old boy; he was born to consanguineous, healthy, and unaffected Turkish parents. He has two elder sisters. The first of them is 10 years old with a diagnosis of MMD. The second sister is 11 years old and healthy without MMD (Fig. 1). He suffered from afebrile focal seizures when he was 11 months old, and seizures were controlled by phenobarbital monotherapy. His cousin also had epilepsy as well. His medical history was normal. The physical examination was normal with height 77 cm (25 percentile for his age) and weight 9 kg (50–75 percentile). The neurological examination revealed moderate paresis in the left upper and lower extremity (muscle strength was a 3/5 in the proximal and distal muscles). He has moderate psychomotor retardation in the Denver Developmental Test. His electroencephalogram (EEG) showed excess slow-wave activity originating from the right temporal region, appearing bilateral parietotemporally in a general distribution. Cerebral MRI showed subacute infarcts in the localization of right frontal and temporal regions. Routine laboratory investigations of the blood were all normal. Hematological investigations of the blood including fibrinogen, antithrombin III, protein C and S, factor VIII and IX level, homocysteine, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), anti-DNA, anticardiolipin antibodies, and antiphospholipid antibodies were all within normal ranges. Methylenetetrahydrofolate reductase 677 C-T, factor V 1691 G-A, and prothrombin 20210 G-A mutations were not detected. Investigations in order to exclude cardiac etiology, electrocardiogram, transthoracic echocardiography, and chest X-ray, were all normal. Cerebral magnetic resonance angiography (MRA) demonstrated irregularity and stenosis of the bilateral distal ICA, proximal middle cerebral artery (MCA), and right proximal posterior cerebral artery (PCA) and an extensive collateral circulation of the lenticulostriate vessels (Fig. 1(1c)). These findings were consistent with MMD. We started enoxaparin, and the patient was investigated for possible mitochondrial disease by our pediatric metabolism department. Finally, the findings of molecular analysis showed a homozygous wild-type

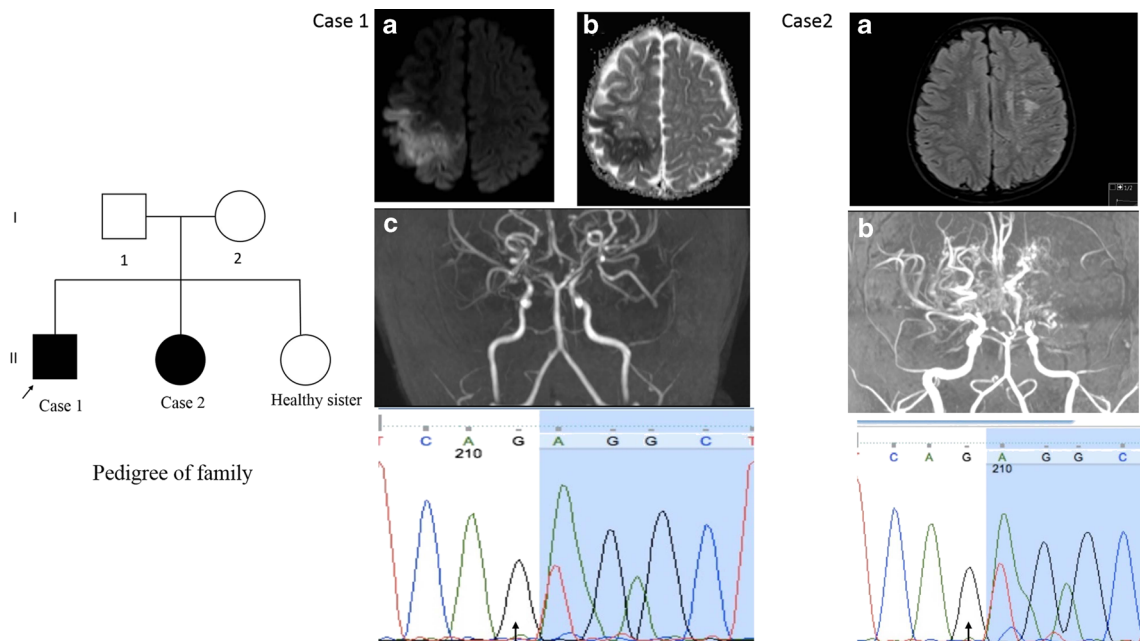


Fig. 1 Family pedigree showing the genotype of c.14576G>A variant. *Black filled square and circle* indicate individuals who are clinically affected with moyamoya disease. *Empty square and circles* show normal individuals. References to specific individuals are shown: the generation number (*Roman numeral*) and position within generation (*Arabic numeral*). The proband of the family is indicated by an *arrow*. Cranial MRI of patient 1 (*1a* and *1b*) is showing new infarcts at the watering area of the right MCA. Cerebral MRA of patient 1 (*1c*) is demonstrating irregularity and stenosis of the bilateral ICA, proximal

MCA, and right proximal PCA and an extensive collateral circulation of the lenticulostriate vessels. Cranial MRI of patient 2 (*2a*) is showing millimetric signal enhancement in the bilateral periventricular white matter without diffusion limitation. Cerebral MRA of patient 2 (*2b*) is demonstrating the narrowing of the left ICA and irregularity and narrowing of the right ICA and an extensive collateral circulation in the localization of bilateral basal ganglions. Electropherogram of the c.14576G>A variant (*arrow*) in RNF213 is also shown. Both patients express the homozygous c.14576G>A variant

c.14576G>A polymorphism in RNF213 gene. Two months later, unfortunately, the patient experienced another focal left-sided seizure and infarct attack. Cranial MRI and MRA showed widespread encephalomalacic changes in the right frontoparietal regions with new infarcts at the watering area of the right MCA; the patient was planned to be operated for indirect revascularization but the family refused (Fig. 1(1a, 1b)). At present, the dosage of enoxaparin was increased and levetiracetam was added for seizure control.

Case 2

Case 2 is a 10-year-old girl who is an elder sister of proband. She was admitted to another state hospital because of headache. Cranial MRI showed isolated left leptomenigeal venous angiomatosis; therefore, she was referred to our pediatric neurology department. The medical history of the patient was unremarkable. Her physical and neurological examination was normal. Cranial MRI showed numerous millimetric signal enhancements in the bilateral periventricular white matter without diffusion limitation and an extensive collateral circulation in the localization of bilateral basal ganglions (Fig. 1(2a)). Routine laboratory, hematological, infectious, and metabolic investigations of blood were all normal. EEG was unremarkable. Electrocardiogram, transthoracic

echocardiography, and chest X-ray were all normal. Cerebral MRA showed stenosis of the left ICA and irregularity and stenosis of the right ICA which were consistent with MMD (Fig. 1(2b)). With these findings, acetylsalicylic acid treatment was started. Genotyping for c.14576G>A variant in exon 61 of RNF213 gene revealed that this girl was wild type for the polymorphism. At present, the patient is being followed up with only acetylsalicylic acid therapy. Clinical, radiologic, and genetic features of both sibling cases are summarized in the Table 1.

Mutational analysis

Genomic DNA from the affected siblings was obtained from peripheral blood leukocytes. The primer sequences and polymerase chain reaction conditions for DNA amplification were referred as described previously [5]. Variant analysis of c.14576G>A (rs112735431) in exon 61 of RNF213 gene was performed by direct sequencing in both of these siblings. As a result, both of these siblings were wild type for c.14576G>A (rs112735431) polymorphism known as the most frequent variant in East Asian patients with moyamoya disease [5, 9] (Fig. 1).

Table 1 Clinical, radiological, and genetic features of sibling cases

Clinical characteristics	Case 1	Case 2
Age at onset (years)	2	10
Transient ischemic attack	+	+
Cerebral infarction	+	–
Seizure	+	–
Psychomotor retardation	Moderate	–
Neurological deficits	+	–
Headache	–	+
Cranial MRI findings	Multiple infarctions	Millimetric signal enhancement without diffusion limitation
Cranial MRA findings		
ICA	Bilateral stenosis	Bilateral stenosis
ACA	–	–
MCA	Bilateral stenosis	–
PCA	Right stenosis	–
Other	–	–
RNF213 genotype	Homozygous c.14576G>A variant in RNF213 gene	Homozygous c.14576G>A variant in RNF213 gene
Surgical treatment	It was suggested but the family refused	–

ICA internal carotid artery, ACA anterior cerebral artery, MCA middle cerebral artery, PCA posterior cerebral artery, MRI magnetic resonance imaging, MRA magnetic resonance angiography

Discussion

Histopathology characteristics of MMD reveal the carotid arteries stenosis or occlusion. The histopathological characteristics of MMD in the carotid termination have shown fibromuscular thickening of the intima, an irregular undulation of the internal elastic lamina, and attenuation of the media [4]. However, the pathogenesis of progressive occlusion of the intracranial ICA and its main branches with formation of vascular network at the base of the brain remains unclear. It is therefore essential to investigate the mechanisms underlying the development and progression in this disease. The list of disorders associated with moyamoya is in continuous expansion. These disorders include neurofibromatosis, Down syndrome, polycystic kidney disease, fibromuscular dysplasia, and meningitis among others [10]. If these conditions are present, moyamoya is named as moyamoya syndrome. The coexistence of these disorders may be associated with an underlying common genetic background predisposing to structural or physiological abnormalities in different tissues and organs. The genetic contribution in MMD is incontestable. The potential role of RNF213 polymorphism on the abnormal cerebral vessels is investigated. Liu et al. [5] demonstrated that zebra fish lacking RNF213 showed irregular wall formation in trunk the arteries and abnormal sprouting vessels in the intracranial and optic vessels. Miyatake et al. [7] reported that patients with the homozygous c.14576G>A variant in the RNF213 gene showed significantly earlier age at onset and wider vasculopathy in the brain, which resulted in a more severe form of MMD. In another study, the researchers [8]

reported that sibling patients of MMD have homozygous and heterozygous c.14576G>A variant in RNF213 with different clinical presentation and discussed its genetic impact on clinical phenotype in members with similar genetic background. However, Hamada et al. [2] reported that pediatric sibling patients of MMD show a tendency towards similar onset age and similar clinical courses and angiographic findings. We report pediatric siblings of MMD who have wild-type homozygosity for c.14576G>A variant in RNF213, showing different clinical course and disease severity (Table 1). Although both of these siblings have wild-type homozygosity for c.14576G>A polymorphism, the first case exhibited significantly earlier onset age and rapid disease progress, which resulted in focal seizures, neurological deficits, and psychomotor retardation. In contrast, the second case exhibited a late-onset age with clinical presentation of headache without irreversible brain lesions. These findings suggest the presence of systemic and environmental factors along with genetic factors for effects on the clinical course and disease severity of MMD. Interestingly, these siblings were born to consanguineous, healthy Turkish parents without MMD phenotype. Whereas consanguinity is not frequent in familial MMD [6].

In conclusion, different clinical severity in pediatric sibling patients of MMD with same doses of polymorphism of the RNF213 gene is first reported. This report supports a multifactorial pathogenesis for the severity of clinical courses in MMD. More investigation will be necessary for contribution to pathogenesis and which factors affect the clinical severity in MMD.

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Authors' contributions UE conceived the study. PH, IM, UH, HK, and DS reviewed the literature; UE, KBA, and YE were involved in patient care, including process of procedure and routine clinical follow-up. UE, YE, and KBA performed literature review and written the manuscript. IM, UH, and HK also made molecular analysis of the patients. PH, IM, and DS also made helpful suggestions to improve the manuscript.

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