Rare *RNF213* variant in adolescent with moyamoya disease

Ivana Cardoso, Mariana Pinto, André Araújo, Marta Vila-Real

Introduction. Moyamoya disease is a progressive steno-occlusive disease of the major intracranial arteries. Affected individuals are at risk for intracranial hemorrhagic or ischemic stroke, cognitive impairment, and developmental delays. Several susceptibility genes have been identified. The p.R4810K variant in the *RNF213* gene has been identified in 95% of patients with familial moyamoya disease.

Case report. We present the case of a 15-year-old adolescent girl who presented with chief complaints of dysgraphia, lack of coordination in the right hand, with two months of evolution. Cerebral magnetic resonance imaging revealed several ischemic lesions with different rates of evolution and magnetic resonance angiography showed multiple subocclusive stenoses. In the study of the sequences of the coding regions and intronic flanking regions (±8 bp) of the *RNF213* gene, the variant c.12185G>A, p.(Arg4062Gln) was detected in heterozygosity in the *RNF213* gene. This result indicates that the patient is heterozygous for the c.12185G>A, p.(Arg4062Gln) variant in the *RNF213* gene. The detected variant has already been reported in the literature as a founder variant in the Asian population, associated with moyamoya syndrome. This variant is described in ClinVar as a variant of unknown clinical significance? Furthermore, it is not described in population databases (dbSNP, ESP, gnomAD).

Conclusion. To our knowledge, the p.(Arg406262Gln) variant has been reported in three Japanese moyamoya disease patients and one European. Therefore, our patient was the second European moyamoya disease patient with this variant identified.

Key words. Arterial occlusive diseases. Genetic databases. Genetic variation. Magnetic resonance angiography. Moyamoya disease. *RNF213* gene.

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Introduction

Moyamoya disease (OMIM 607151) is a progressive steno-occlusive condition of the main intracranial arteries [1]. It is characterized by progressive bilateral and occasional unilateral stenosis and occlusion of the distal internal carotid artery, with frequent involvement of the middle and anterior cerebral arteries [2]. This results in the compensatory formation of fragile moyamoya vessels at the base of the brain, which resembles 'puffs of smoke' [1,3].

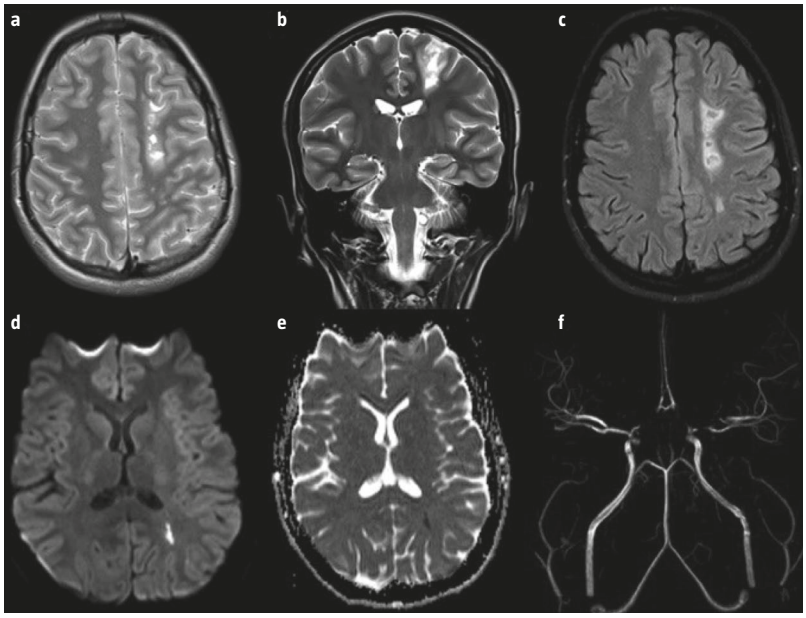
Affected individuals are at risk of intracranial hemorrhagic or ischemic stroke, seizures, cognitive impairment, and developmental delays [2]. Extracranial vascular involvement, such as the one concerning the renal arteries, has often been reported [1].

Moyamoya disease occurs worldwide, with highest prevalence in East Asian countries [2]. The annual incidence of moyamoya disease is estimated to be 0.35 ± 0.94 per 100,000 people in Japan, and approximately one-tenth of that number in Europe [4].

Several susceptibility genes have been identified, such as *RNF213* (NM_001256071.2; chr. 17), *ACTA2* (NM_001613.2; chr. 10) and *GUCY1A3*, the latter being linked to moyamoya disease with achalasia [4]. *RNF213* is the most significant susceptibility gene, some of its variants were illustrated as susceptibility variants for moyamoya disease and non-moyamoya intracranial artery stenosis/occlusion disease [1,2]. The p.R4810K variant in the *RNF213* gene is the foremost susceptibility variant for moyamoya disease in East Asian patients and is also associated with moyamoya syndrome. Moyamoya syndrome is considered a moyamoya vasculopathy observed in specific disorders, such as neurofibromatosis type 1[1,5].

Variant p.Arg4810Lys has been identified in 95% of patients with familial moyamoya disease, as well as in 80% of patients with sporadic moyamoya disease. Several *RNF213* non-p.Arg4810Lys variants

Figure 1. a) Axial T_2/TSE showing the multiple ischemic lesions in watershed territory of the left middle cerebral artery; b) and c) Coronal T_2/TSE and axial FLAIR showing the same lesions; d) and e) diffusion weighted imaging and apparent diffusion coefficient map showing acute periventricular left parietal ischemic lesion; f) Magnetic resonance angiography showing multiple intracranial stenosis involving the supraclinoid segments of the internal carotid arteries, the A1 segments and the left M1 segment of the middle cerebral artery.



have recently been found in Caucasian and East/South Asian cases of moyamoya disease. However, clinical manifestations and angiographic findings differ between Caucasian and East Asians. Variant p.R4062Q has been reported in four patients with moyamoya disease among one European and two Japanese families and it is, therefore, regarded as the second most significant mutation for moyamoya vasculopathy [4,5]. Recent reports have demonstrated the presence of severe clinical manifestations in patients who presented rare deleterious variants in *RNF213* other than p.R4810K, such as in patients with p.S3986N or p.R4062Q [5]. To date, mechanisms through which RNF213 p.R4810K and other rare variants lead to intracranial vascular lesions are still unknown [2]. Epidemiological and genetic studies have demonstrated that moyamoya disease is a multifactorial disease. The recurrence rates in relatives were markedly lower than those expected from simple mendelian inheritance. It is believed that the susceptibility variants of *RNF213* require additional environmental or genetic factors for the development of moyamoya disease [1].

Case report

We report the case of a 15-year-old teenager with no significant personal history nor significant family history and no consanguinity.

She presented with chief complaints of dysgraphia, lacking coordination in the right hand, with two months of evolution. There were no other complaints nor any history of infection or trauma. She had started combined oral contraceptive pill at the time of the complaints. The patient was not under other medication and had no smoking habits. On objective examination on admission, mild dysgraphia was visible. The remaining neurological examination revealed no language disorders. For instance, she named and repeated well everything requested, with a slight decrease in fluency regarding words beginning with 'P'. There was no apraxia and no changes in visual fields, oculomotricity or facial mimicry. No motor or sensory deficits were found nor gait alterations. The patient was observed by the ophthalmology unit, with normal results.

Regarding complementary diagnostic tests, a brain magnetic resonance was performed, revealing several ischemic lesions with different paces of evolution, involving the cortico-subcortical fronto-parietal region on the left, with extension throughout the *centrum semiovale*, suggesting watershed infarcts (Fig. 1). Magnetic resonance angiography showed multiple subocclusive stenosis of both supra-clinoid segments of the internal carotid arteries, both A1 segments, and also the M1 segment of the left middle cerebral artery (Fig. 1). Laboratorial studies showed no relevant alterations, with complete blood count, renal and hepatic function and lactate dehydrogenase presenting no changes. There was no dyslipidemia, a normal homocysteine value, and an unremarkable immunological study, including negative antiphospholipid and antinuclear antibodies, as well as rheumatoid factor. The coagulation study was normal, and through a prothrombotic study, common polymorphism of methylene tetrahydrofolate reductase was found. Furthermore, there were normal levels of plasminogen activator inhibitor-1. Cerebrospinal fluid presented normal cytochemistry, negative bacteriology and positive cytomegalovirus polymerase chain reaction with intermediate cycle threshold value. Serum immunoglobulin G were positive and immunoglobulin M were negative. Cytomegalovirus DNA research in serum negative. It was decided to start ganciclovir and intravenous corticosteroid.

Cytomegalovirus research was requested in the cerebrospinal fluid by specific real-time polymerase

chain reaction for cytomegalovirus, and it came back negative. This way, the patient completed six days of treatment with antivirals. Oligoclonal bands in cerebrospinal fluid dis not present any changes. A vessel wall magnetic resonance imaging was performed for further investigation. There was slight increase in T_1 signal after gadolinium in the vessel wall along the left M1 segment, corresponding to the point of focal stenosis, with no increase of vessel wall thickness (Fig. 2). There were no other abnormal focal areas of enhancement involving the remaining intracranial vessels. These changes favored primary moyamoya disease rather than a secondary etiology, namely vasculitis. Conventional cerebral angiography was performed, showing significant stenosis of the right A1 segment and irregularities of the left M1 segment (with decrease in the distal flow), occlusion of the left A1 segment, with some degree of collateralization, through pial vessels of the left middle cerebral artery. The presence of moyamoya type vessels was not observed (Fig. 3).

During hospitalization, persistent high blood pressure values were noted. An electrocardiogram, an echocardiogram, renal echo-Doppler and computed tomography angiography of the renal arteries were also requested, which were unremarkable, with the patient presenting normal values of aldosterone, activated renin, and plasma metanephrines.

With moyamoya disease panel massive sequencing in progress, our patient was discharged from the hospital under treatment with acetylsalicylic acid and angiotensin-converting enzyme inhibitor. Also, combined oral contraceptive pill was suspended and she was oriented for multidisciplinary follow-up.

In the sequencing study of the coding regions and flanking intronic regions (±8 bp) of the *ACTA2* gene, no mutations were detected in the regions analyzed. In addition, in the study of coding regions sequences and flanking intronic regions (±8 bp) of the *RNF213* gene, the variant c.12185G>A, p.(Arg4062Gln) was detected in heterozygosity in the *RNF213* gene. This result indicates that the patient is heterozygous for the variant c.12185G>A, p.(Arg4062Gln) in the *RNF213* gene. The variant detected is already reported in the literature as a founder variant in Asian population, associated with moyamoya syndrome. This variant is described in ClinVar as a variant of unknown clinical significance. Additionally, it is not described in population databases (dbSNP, ESP, gnomAD) and affects a highly conserved amino acid. With the available information, this variant should be classified as probably pathogenic. Studying the patient's parents allowed to conclude that the detected variant was inherited from the father.

Approximately four months after discharge, cerebral magnetic resonance angiography was repeated, revealing worsening of the intracranial stenosis, namely with a new stenosis of left P1 segment of

Figure 2. a) Axial T_2/SE with black blood suppression, showing the focal stenosis of the left M1 segment, with no increase in the thickness of the vessel wall; b) Axial T_1/SE with black blood suppression with no focal areas of T_1 hyper-intensities; c) Axial T_1/SE BBS with gadolinium depicting the focal area of signal increase involving the focal stenosis of the left M1; d) and e) Sagittal and coronal T_1/SE BBS with gadolinium showing the focal area of increased signal, not forming the complete ring typical of vasculitis.

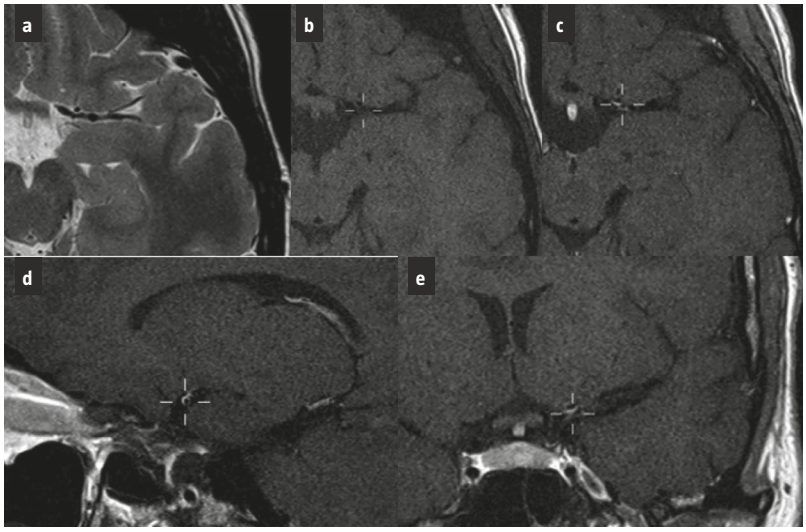
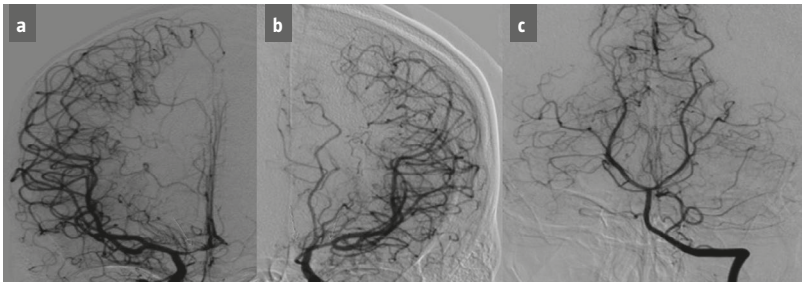


Figure 3. a) Right internal carotid artery injection showing stenosis of the supraclinoid segment and the A1 segment. b) Left internal carotid artery injection depicting occlusion of the A1 segment and stenosis of the supraclinoid and M1 segments. c) Left vertebral artery injection, with no focal stenosis involving the posterior fossa circulation, which is typical of moyamoya disease.



the posterior cerebral artery (figures not included). Therefore, the angiotensin-converting enzyme inhibitor was suspended. Three years after initial hospitalization, our patient underwent elective surgery for indirect cerebral revascularization, encephaloduromyosinangiosis. Both the surgery and the postoperative period were uneventful. Currently, about five months after surgical intervention, she remains asymptomatic, under treatment with acetylsalicylic acid and maintaining follow-up.

Discussion

Moyamoya disease is a rare idiopathic intracranial vascular disorder with strong genetic components. Genetic study of familial moyamoya disease clearly indicated autosomal dominant inheritance pattern [2], which is in accordance with our case, since this variant was identified in our patient's father. However, the penetrance of autosomal dominant moyamoya disease is low, as illustrated by discordant identical twins or 'skipping a generation' [3;4].

To the best of our knowledge, p.(Arg4062Gln) variant has been reported in three Japanese moyamoya disease patients and in one European. Therefore, our patient was the second European with moyamoya disease with this variant identified. The presentation of the disease was variable in the reported cases. In contrast to our patient, the European patient with the same identified *RNF213* gene variant had a hemorrhagic stroke as clinical presentation [1].

It is important to accumulate improved knowledge about the variously reported *RNF213* variants in moyamoya disease patients since there is little information on genotype–phenotype correlation [1]. Studies focused on delineating the ethnicity-specific factors and pathological role of *RNF213* variants in moyamoya disease and intracranial artery stenosis/occlusion disease are needed. Unknown factors are considered to overlay the genetic predisposition to develop moyamoya. In this case, the patient's father has not shown any symptoms until the current moment.

There is no medication that can inhibit or reverse moyamoya disease progression. At present, direct or indirect neurosurgical revascularization is the mainstay treatment for the symptoms of moyamoya disease, such as repeated transient ischemic attack, and it prevents not only subsequent ischemic attacks but also intracranial haemorrhage [2,3]. With this case report, we present a patient who underwent elective surgery for indirect cerebral revascularization.

Pathological clues for early diagnosis and novel therapeutic approaches are needed [2].

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Variente rara de *RNF213* en adolescente con enfermedad de moyamoya

Introducción. La enfermedad de moyamoya es una enfermedad estenooclusiva progresiva de las principales arterias intracraneales. Los individuos afectados corren el riesgo de sufrir un accidente cerebrovascular hemorrágico o isquémico intracraneal, deterioro cognitivo y retrasos en el desarrollo. Se han identificado varios genes de susceptibilidad. La variante p.R4810K en el gen *RNF213* se ha identificado en el 95% de los pacientes con enfermedad de moyamoya familiar.

Caso clínico. Presentamos el caso de una adolescente de 15 años que se presentó con quejas principales de disgrafía y falta de coordinación en la mano derecha con dos meses de evolución. La resonancia magnética cerebral reveló varias lesiones isquémicas con diferentes ritmos de evolución y la angiorresonancia magnética mostró múltiples estenosis suboclusivas. En el estudio de las secuencias de las regiones codificantes y de las regiones intrónicas flanqueantes (±8 pb) del gen *RNF213,* se detectó la variante c.12185G>A, p.(Arg4062Gln) en heterocigosidad en el gen *RNF213.* Este resultado indica que la paciente es heterocigota para la variante c.12185G>A, p.(Arg4062Gln) en el gen *RNF213.* La variante detectada

ya ha sido descrita en la bibliografía como una variante fundadora en la población asiática, asociada a síndrome de moyamoya. Esta variante está descrita en ClinVar como una variante de significado clínico desconocido. Además, no está descrita en las bases de datos poblacionales (dbSNP, ESP y gnomAD).

Conclusión. Hasta donde sabemos, la variante p.(Arg4062Gln) se ha notificado en tres pacientes japoneses con enfermedad de moyamoya y en uno europeo. Por lo tanto, nuestro paciente fue el segundo europeo con enfermedad de moyamoya con esta variante identificada.

Palabras clave. Angiografía por resonancia magnética. Bases de datos genéticas. Enfermedad de moyamoya. Enfermedades arteriales oclusivas. Gen *RNF213*. Variaciones genéticas.