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FULL LENGTH ARTICLE

Autosomal recessive cerebellar ataxia with spasticity due to a rare mutation in *GBA2* gene in a large consanguineous Saudi family

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Abstract The nonlysosomal glucosylceramidase β2 (*GBA2*) gene encode an enzyme that catalyzes the hydrolysis of glucosylceramide to glucose and ceramide. Mutations in the *GBA2* gene have been reported to cause hereditary spastic paraplegia, autosomal recessive cerebellar ataxia with spasticity, and Marinescu-Sjögren-Like Syndrome. In this study, we report the clinical features and genetic diagnosis of autosomal recessive cerebellar ataxia with spasticity due to a rare mutation in *GBA2* gene in a large consanguineous Saudi family. We included a large consanguineous Saudi family with a presumptive clinical diagnosis of ataxia at King Abdulaziz Medical City in Jeddah, Saudi Arabia. The family included six affected individuals and four unaffected in addition to the parents. Whole exome sequencing (WES) was performed for the proband IV-5, and Sanger sequencing was used to confirm the variant in other family members. Segregation study was performed using DNA from the parents and siblings of the proband. Sequence analysis identified a homozygous variant c.2618G>A, p.(Arg873His) in *GBA2* gene. The homozygous variant was identified in affected

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members of the family while the parents and the other four siblings were heterozygous carriers of the variant. One sibling was not available for genetic testing. The variant identified in our patients is classified as pathogenic considering the current evidence of the variant. Autosomal recessive cerebellar ataxia with spasticity is an extremely rare genetic disorder with very few cases reported in the literature. We conclude that the c.2617G>A mutation in *GBA2* gene causes the loss of function with abolishment of the enzymatic activity that causes the disease. This report adds further evidence to support the pathogenicity of this variant. The patients had the classical clinical phenotype of cerebellar ataxia and spasticity consistent with previous reports in the literature.

Introduction

Hereditary spinocerebellar ataxias are rare neurodegenerative disorders characterized by progressive degeneration of the cerebellar Purkinje cells and spinocerebellar tracts.[1] The typical clinical manifestation of these disorders is ataxia with impaired walking and lack of gait and limb coordination.[2] This feature may be accompanied with other upper motor neuron signs such as increased tone in the limbs which may progress to pronounced limb spasticity.[3] Mutations in the glucosylcerebrosidase 2 (*GBA2*) gene have been reported to cause hereditary spastic paraplegia,[4] autosomal recessive cerebellar ataxia with spasticity,[5] and Marinescu-Sjögren-Like Syndrome.[6] In this study, we report the clinical features and genetic diagnosis of autosomal recessive cerebellar ataxia with spasticity due to a rare mutation in *GBA2* gene in a large consanguineous Saudi family.

Methods

We included a large consanguineous Saudi family with a presumptive clinical diagnosis of ataxia at King Abdulaziz Medical City in Jeddah, Saudi Arabia. The family included six affected individuals and four unaffected in addition to the parents (Fig. 1). All family members were examined physically, neurologically, psychiatrically, and questioned about their daily activities. In addition, affected patients had basic blood work and magnetic resonance imaging (MRI) of the brain. All patients had the same clinical phenotype. The entire family was consented for genetic testing after explanation of pros and cons of such investigations. Whole exome sequencing (WES) was performed for the proband IV-5, and Sanger sequencing was used to confirm the variant in other family members. Segregation study was performed using DNA from the parents and the siblings of the proband. This study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC).

Case report

Proband IV-5 is a 32-year-old female who was previously healthy until the age of 12 years old when she started to develop imbalance, frequent falls, and difficulty in mobilization. The course of her disease was gradually progressive with later on involvement of speech and vision. She had dysarthria with depression due to difficulties in comprehension and communication. She also had difficulty focusing with blurring of vision and difficulty reading. She had a strong family history of a similar condition. Her past medical history was unremarkable for trauma, endocrinopathy, exposure to drugs or toxins, or systemic malignancy. Clinically, the patient had florid cerebellar and pyramidal tract signs including nystagmus, staccato speech,

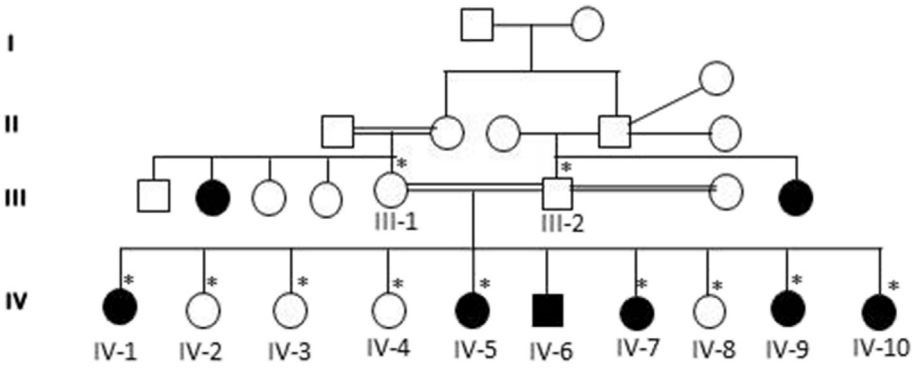

Figure 1 Pedigree of the members after detailed family history. The available samples are marked with an asterisk sign.

dysmetria, dysdiadochokinesia, and impaired regular and tandem gait. She also had bilateral action tremors, head titubation, and truncal ataxia. In addition, she had symmetrical spasticity of both upper and lower extremities with brisk reflexes and bilateral Babinski sign. Her routine basic biochemical and hematological screen were unremarkable including vitamin E level and thyroid function test. MRI of the brain showed mild cerebellar atrophy with special involvement of cerebellar medline structures (Fig. 2). She was managed with physiotherapy, occupational therapy, and genetic counseling. She is booked for stem cell therapy in the near future.

Results

Sequence analysis identified a homozygous variant c.2618G > A, p.(Arg873His) in *GBA2* gene. This missense variant is absent in the Genome Aggregation Database (gnomAD, $n > 120{,}000$ exomes and >15,000 genomes). The variant is predicted deleterious by *in silico* prediction tools, and it is located within the C-terminal region (residues 500—886), a region conserved across species. The homozygous variant was identified in four of her siblings while the parents and the other four siblings were heterozygous carriers of the variant. One sibling was not available for genetic testing (Fig. 3). The variant identified in our patients is classified as pathogenic considering the current evidence of the variant (established association between the gene and the patient's phenotype, rarity in control populations, *in silico* predicted pathogenicity, functional assay data, identification of the variant in either homozygous or compound heterozygous state in two families with cerebellar ataxia or spastic paraplegia, respectively). Mutation nomenclature is based on GenBank accession NM_020944.2 (*GBA2*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

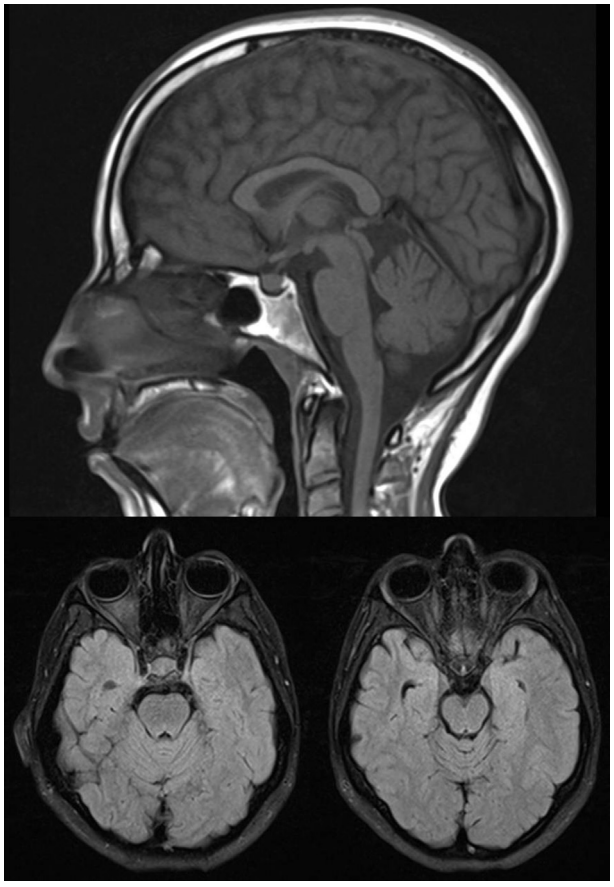

Figure 2 MRI of the brain showing mild cerebellar atrophy with special involvement of cerebellar medline structures.

Discussion

The *GBA2* gene (MIM: 609471) on chromosome 9p13.3 encodes a microsomal nonlysosomal beta-glucosidase that is localized on plasma membrane and endoplasmic reticulum. Beta-glucosidase 2 is a ubiquitous enzyme available in all human tissues and maximally expressed in the brain, heart, kidney, placenta, and skeletal muscles. The enzyme catalyzes the conversion of glucosylceramide to free glucose and ceramide, and the hydrolysis of bile acids 3-D-glucosides.[7] The activity of the *GBA2* is linked to sphingomyelin generation and prevention of glycolipid accumulation, which is important for the development of central nervous system.[8]

The c.2618G > A, p.(Arg873His) variant has been previously reported in association with cerebellar ataxia with spasticity and spastic paraplegia. It has been reported in a homozygous state in two affected siblings of a consanguineous family with cerebellar ataxia with spasticity.[9] In addition, it has been reported in a compound heterozygous state with p.(Arg630Trp) in a family with two affected siblings with disease onset in infancy/childhood and a complex phenotype with cerebellar signs and ataxic gait.[10] Functional studies have identified that this variant resulted in reduced enzyme activity in transfected cells.[11] This variant has an entry in ClinVar (ID 41490). It is also of note that another variant affecting the same amino acid residue, p.(Arg873Cys), has been reported in association with autosomal recessive spastic paraplegia-46.[12]

The new advances in genetic diagnostic processes such as next-generation sequencing have recently revolutionized the clinicogenetic distinction between hereditary cerebellar ataxias and hereditary spastic paraplegia.[13] Although the clinical, pathological, radiological, and genetic distinction between these two disorders is sometimes easy and straight forward, the distinction is difficult in certain conditions. This led to the introduction of a new concept of spastic ataxia phenotypic spectrum rather than referring to them as two separate diseases[14] (Table 1).

Stem cell therapy is an attractive treatment option for patients with neurodegenerative disorders due to its theoretical potential and excellent expected outcomes.[15] Several forms of stem cell therapy have been tested in preclinical models and showed promising results.[16] However, its use is limited due to lack of high-quality, large-scale studies addressing several aspects of therapy including safety, mode of administration, frequency of administration, and efficacy.[17] A recent phase I/IIa clinical trial reported the safety and possible efficacy during the 1-year follow-up after intravenous administration of stem cells for patients with spinocerebellar ataxia.[18] In addition,

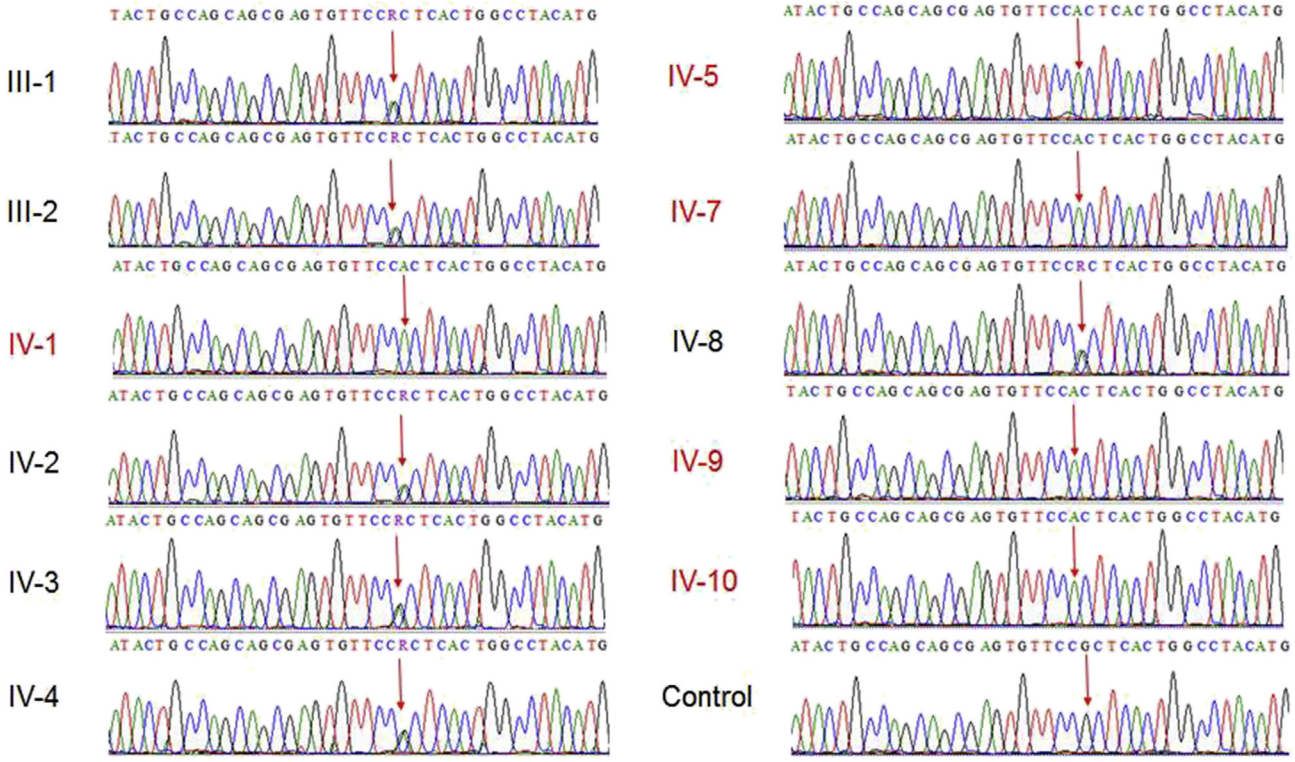

Figure 3 Representative chromograph of *GBA2* Sanger sequencing read of all family members. Genetic analysis identified this variant in the proband IV-5 and four of her siblings. In addition, the other affected family members were heterozygous carriers of this variant.

Table 1 The differences between hereditary cerebellar ataxia and hereditary spastic paraplegia.

	Hereditary cerebellar ataxia	Hereditary spastic paraplegia
Epidemiology	Approximately 1—9 in 100,000 people	Approximately 2—6 in 100,000 people
Pathology	Purkinje cells and/or spinocerebellar tract involvement combined with atrophy of brainstem or other regions of the nervous system	Pyramidal tract degeneration accompanied by posterior cordonal tract impairment
Etiological Mechanism	Neuronal loss in the cerebellum	Distal axonal degeneration of the longest tract within the central nervous system
Mode of Inheritance	Mostly inherited through autosomal dominant and recessive transmission but all the known inheritance patterns are observed	Mostly inherited through autosomal dominant and recessive transmission but all the known inheritance patterns are observed
Clinical Features	Cerebellar syndrome with progressive gait and limb ataxia, loss of coordination, nystagmus and other oculomotor control signs, and dysarthria	Pyramidal signs with pyramidal weakness in the lower limbs, spasticity, hyperreflexia, and bilateral upgoing toes
Radiological Characteristics	Atrophy of the cerebellum is a relatively constant finding. Extracerebellar regions are also affected depending on the specific type of ataxia	Non-specific and variable findings, which include corpus callosum atrophy, increased T2 signal intensity in the posterior limb of the internal capsule, spinal cord atrophy, and ears of the lynx sign (high T2/FLAIR signal intensity at the tip of the frontal horns of the lateral ventricles)

another study showed no serious transplant-related adverse events to intravenous and intrathecal infusion of allogeneic umbilical cord mesenchymal stromal cells with the majority of patients showing clinical improvement continuing for at least six months.[19] Further research is expected to be published in the near future and carries hope for patients with hereditary ataxias.[20] Our patient elected to go for stem cell therapy in the near future with the hope to

improve her symptoms or even possibly cure her disease. Another follow-up study reporting the outcome of her treatment may be published in the future.

Conclusion

Autosomal recessive cerebellar ataxia with spasticity is an extremely rare genetic disorder with very few cases reported in the literature. In this study, we reported a rare homozygous variant c.2618G > A, p.(Arg873His) in the *GBA2* gene in a large consanguineous Saudi family. We conclude that the c.2617G > A mutation in *GBA2* gene causes the loss of function with abolishment of the enzymatic activity that causes the disease. This report adds further evidence to support the pathogenicity of this variant. The patients had the classical clinical phenotype of cerebellar ataxia and spasticity consistent with previous reports in the literature. Hereditary ataxia with spasticity remains challenging to manage with no successful therapeutic options to date. Further studies focusing on possible therapeutic interventions such as stem cell therapy are highly encouraged.

Conflict of Interests

The authors declare that they have no conflicts of interest.

References

1. Paulson HL. The spinocerebellar ataxias. *J Neuro Ophthalmol*. 2009;29(3):227—237.
2. Brusse E, Maat-kievit JA, Van swieten JC. Diagnosis and management of early- and late-onset cerebellar ataxia. *Clin Genet*. 2007;71(1):12—24.
3. Ashizawa T, Xia G. Ataxia. *Continuum (Minneap Minn)*. 2016; 22(4 Movement Disorders):1208—1226.
4. Coarelli G, Romano S, Travaglini L, et al. Novel homozygous GBA2 mutation in a patient with complicated spastic paraplegia. *Clin Neurol Neurosurg*. 2018;168:60—63.
5. Votsi C, Zamba-papanicolaou E, Middleton LT, Pantzaris M, Christodoulou K. A novel GBA2 gene missense mutation in spastic ataxia. *Ann Hum Genet*. 2014;78(1):13—22.
6. Haugarvoll K, Johansson S, Rodriguez CE, et al. GBA2 mutations cause a Marinesco-Sjögren-like syndrome: genetic and biochemical studies. *PLoS One*. 2017;12(1), e0169309.
7. Woeste MA, Wachten D. The enigmatic role of GBA2 in controlling locomotor function. *Front Mol Neurosci*. 2017;10:386.
8. Boot RG, Verhoek M, Donker-koopman W, et al. Identification of the non-lysosomal glucosylceramidase as beta-glucosidase 2. *J Biol Chem*. 2007;282(2):1305—1312.
9. Hammer MB, Eleuch-fayache G, Schottlaender LV, et al. Mutations in GBA2 cause autosomal-recessive cerebellar ataxia with spasticity. *Am J Hum Genet*. 2013;92(2):245—251.
10. Morais S, Raymond L, Mairey M, et al. Massive sequencing of 70 genes reveals a myriad of missing genes or mechanisms to be uncovered in hereditary spastic paraplegias. *Eur J Hum Genet*. 2017;25(11):1217—1228.
11. Sultana S, Reichbauer J, Schüle R, Mochel F, Synofzik M, Van der spoel AC. Lack of enzyme activity in GBA2 mutants associated with hereditary spastic paraplegia/cerebellar ataxia (SPG46). *Biochem Biophys Res Commun*. 2015;465(1):35—40.
12. Yang YJ, Zhou ZF, Liao XX, et al. SPG46 and SPG56 are rare causes of hereditary spastic paraplegia in China. *J Neurol*. 2016;263(10):2136—2138.
13. Parodi L, Coarelli G, Stevanin G, Brice A, Durr A. Hereditary ataxias and paraparesias: clinical and genetic update. *Curr Opin Neurol*. 2018;31(4):462—471.
14. Synofzik M, Schüle R. Overcoming the divide between ataxias and spastic paraplegias: shared phenotypes, genes, and pathways. *Mov Disord*. 2017;32(3):332—345.
15. Mukai T, Tojo A, Nagamura-inoue T. Mesenchymal stromal cells as a potential therapeutic for neurological disorders. *Regen Ther*. 2018;9:32—37.
16. Chang KA, Lee JH, Suh YH. Therapeutic potential of human adipose-derived stem cells in neurological disorders. *J Pharmacol Sci*. 2014;126(4):293—301.
17. Forostyak S, Jendelova P, Sykova E. The role of mesenchymal stromal cells in spinal cord injury, regenerative medicine and possible clinical applications. *Biochimie*. 2013;95(12): 2257—2270.
18. Tsai YA, Liu RS, Lirng JF, et al. Treatment of spinocerebellar ataxia with mesenchymal stem cells: a phase I/IIa clinical study. *Cell Transplant*. 2017;26(3):503—512.
19. Jin JL, Liu Z, Lu ZJ, et al. Safety and efficacy of umbilical cord mesenchymal stem cell therapy in hereditary spinocerebellar ataxia. *Curr Neurovasc Res*. 2013;10(1):11—20.
20. Buijsen RAM, Toonen LJA, Gardiner SL, Van roon-mom WMC. Genetics, mechanisms, and therapeutic progress in polyglutamine spinocerebellar ataxias. *Neurotherapeutics*. 2019;16(2): 263—286.