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Hispanic Spinocerebellar Ataxia type 35 (SCA35) with a Novel Frameshift Mutation

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Abstract

Genetic mutations in transglutaminase 6 (*TGM6*) are recently identified to be associated with spinocerebellar ataxia type 35 (SCA35). We report a Hispanic SCA35 patient, who was confirmed to have a heterozygous, single-nucleotide deletion in *TGM6*, causing a frameshift mutation with a premature stop codon. An immune-mediated ataxia previously found to be associated with autoantibody reactivity to TG6 may share a similar pathomechanism to SCA35, suggesting a converging role for TG6 in cerebellar function.

Keywords

Spinocerebellar ataxia; SCA35; Gluten; Cerebellum; transglutaminase; *TGM6*

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CCL: examined the patient, reviewed his medical records, searched literature and wrote the first draft of the manuscript.

SRG: examined the patient, reviewed his medical records and critically reviewed the manuscript.

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AA: performed TG6, TG2, and gliadin antibody assays and critically reviewed the manuscript.

PG: examined the patient, performed endoscopy, and critically reviewed the manuscript. SHK: examined the patient, reviewed his medical records and critically reviewed the manuscript.

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Informed consent for videotaping and publishing the video for academic purposes was obtained from the subject reported in this article.

Introduction

Spinocerebellar ataxias (SCAs) are autosomal-dominant diseases that primarily affect the cerebellar function. There are more than 40 types of SCAs and among them, the responsible genetic mutations in more than 30 types have been identified. SCA35 patients typically present with progressive gait instability, scanning speech, and poor dexterity in hands. There are also reports of extraocular movement limitations and tremor. Clinically, there is no specific defining feature to distinguish SCA35 from other SCAs. Recently, through whole-exome sequencing and segregation analysis, mutations in *TGM6* were confirmed to be the cause of SCA35 [1, 2]. Transglutaminases (TGs) are a group of proteins that catalyze reactions to crosslink the amide group of glutamine with the amino group of lysine as well as deamidate glutamine (if the acceptor group is water instead of amine) [3]. Gluten proteins of wheat and related cereals are rich in glutamine residues, making them potential substrates for TGs [4]. Antibodies against TG6 have been found in cases of ataxia in conjunction with immune reactivity to gluten (referred to as gluten ataxia), which may improve with a gluten-free diet [5–8]. The mechanism of *TGM6* mutations causing cerebellar ataxia is still unclear, but the involvement of TG6 in both SCA35 and gluten ataxia raises the possibility of a shared mechanism between the two. We report a Hispanic SCA35 patient with a family history of ataxia. He has a heterozygous, single-nucleotide deletion in *TGM6*, which is predicted to produce a truncated TG6 protein or result in nonsense-mediated decay at the mRNA level. Interestingly, the patient had stabilization, if not slight improvement, of his ataxia after adopting a gluten-free diet, supporting the possibility of a converging mechanism for gluten ataxia and SCA35.

Case Presentation

We present a 63-year-old right-handed Hispanic man from Puerto Rico who developed progressive gait instability and slurred speech since age 40. He did not have gastrointestinal symptoms, arthritis, cognitive decline, muscle weakness, or numbness. Two of his four brothers and his mother also had gait abnormalities and a diagnosis of cerebellar ataxia (Figure 1). On examination, he had scanning speech, dysmetria in finger-nose-finger, finger-chase, and knee-shin slide tests as well as impaired rapid alternative movements. In addition, he had mild rigidity and bradykinesia in the neck and upper extremities. His reflexes were brisk throughout with down-going toes. He had normal muscle strength and intact sensation to pinprick, vibration, and proprioception. He had a wide-based gait with variable stride length. No pigmentary retinal degeneration was noted on his examination. His scale for the assessment and rating of ataxia (SARA) score was 21 at the initial visit. His brain magnetic resonance imaging showed marked cerebellar atrophy. He had normal levels of anti-gliadin (IgG and IgA), anti-TG2 (IgA), and anti-TG6 (IgG and IgA) antibodies. His duodenal biopsy revealed normal mucosa without evidence of celiac disease. According to Harding classification, he fits autosomal-dominant cerebellar ataxia type 1 [9]. Targeted genetic tests for autosomal-dominant ataxia genes, including *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *ATXN8OS*, *ATXN10*, *TBP* and *ATN1* showed no pathological repeat expansions. Whole-exome sequencing revealed a 1-base-pair deletion in *TGM6* (c.841, exon 6) in the heterozygous state, resulting in a frameshift mutation and a premature stop codon. Therefore, it may produce a truncated protein with only 289 amino acids or be subjected to

nonsense-mediated decay at the mRNA level (predicted by SIFT, Sorting Intolerant From Tolerant, and MutationTaster, original length 706 amino acids). The mutation in *TGM6* confirms the diagnosis of SCA35. Interestingly, anti-TG6 antibodies have been found to be elevated in cases of gluten ataxia, with a potential pathogenic role [10, 11]. Given that TG6 is linked to both gluten ataxia and SCA35, there may be a convergence of pathomechanisms between the two. A similar case where immunological and genetic mechanisms meet is myasthenic syndrome. Importantly, acquired myasthenia gravis, caused by autoantibodies against acetylcholine receptor (AChR), and congenital myasthenic syndrome due to AChR deficiency both can respond to cholinesterase inhibitors. We thus hypothesized that the treatment for gluten ataxia, a gluten-free diet, may also be beneficial to SCA35 patients. Our patient was treated with gluten-free diet, and his total SARA score showed a trend of slight improvement (20.5 at baseline immediately before starting gluten-free diet to 18 and 19 at month 5 and 8, respectively), predominantly in the scores of hand dysmetria (See Table 1 and Video segment 1). At month 15, his SARA score was 18.5, suggesting the possibility of long-term stabilization of his ataxia symptoms with gluten-free diet.

Discussion

A total of 14 mutations in *TGM6*, including our present case, have been reported to cause SCA35 (Table 2) [1, 2, 12–14]. Ten of them are missense mutations, one leads to deletion of a glutamate, one has duplication of a glutamine, and one is a splice-site mutation, predicted to alter splicing of *TGM6* pre-mRNA. Our patient has a single-nucleotide deletion (c.841) in the exon 6 of *TGM6*. The resulting frameshift mutation causes a premature stop codon, thus producing a truncated TG6 protein that is predicted to miss the majority of the domain harboring the transglutaminase active sites. In addition, there may be nonsense-mediated decay of the aberrant mRNA, preventing a protein product altogether (predicted by SIFT). Seven of the known mutations were confirmed to have reduced transglutaminase activity, while four showed no significant reduction of their enzymatic activities, and two were not studied (Table 2) [13]. Mutations of TG6 have been proposed to cause neuronal damage through mechanisms including loss of enzymatic activity, change in subcellular distribution, sensitization to apoptosis, accumulation of misfolded TG6, and shortened half-life of mutant TG6 [13, 15]. Variable alterations of protein function from different mutations may partly explain the variability of clinical presentations, and may suggest heterogeneity of pathomechanisms through mutant TG6. Half of the known mutations have reduced transglutaminase activity, implicating enzymatic activity of TG6 may be important in the pathogenesis of SCA35, at least in a subgroup of patients. Identifying TG6 substrates and further studying their presence in postmortem pathology and animal models will provide additional insights.

Interestingly, anti-TG6 antibodies are associated with gluten ataxia and patients adopting gluten-free diet showed clinical improvement with a corresponding decrease in levels of anti-TG6 antibodies in previous studies [5–8]. The possibility of a shared mechanism through gluten-TG6 interaction between genetic and immune-mediated ataxias led us to try gluten-free diet on our SCA35 patient. His SARA score showed a trend of improvement and possibly long-term stabilization after the institution of a gluten-free diet. There is no information regarding the natural history in SCA35 patients, but affected family members of

our patient eventually become wheelchair-bound, suggesting a progressive course. Our single-case report is far from conclusive for the gluten-free diet to treat SCA35. More cases with long-term follow up will be needed to either confirm or refute the therapeutic benefits.

SCA35 was first discovered in the Han-Chinese population and was subsequently confirmed in other Chinese ataxia families [1, 2, 14] as well as Taiwanese ataxia families with Han-Chinese ancestry [12], initially raising the questions whether SCA35 has prominent founder effects and thus may be population-specific. A recent study screened 963 patients with undiagnosed hereditary SCAs at institutions in France, United Kingdom, and United States found novel *TGM6* mutations in patients of Asian and European descents [13]. Our case also demonstrated that SCA35 can occur in Hispanic ethnicity. Another study screened Chinese patients with undiagnosed sporadic ($n = 102$) and familial ($n = 75$) cerebellar ataxias, finding 2 novel *TGM6* mutations, one in the sporadic group and one in the autosomal-dominant familial group [14]. These studies suggest that SCA35, although rare, should be included in clinical consideration for both sporadic and familial ataxias, regardless of the ethnicity.

In summary, we here report a Hispanic SCA35 case, which also provides important insight into the understanding of *TGM6* and familial ataxia. In addition, gluten-free diet may stabilize, if not slightly improve, clinical symptoms in SCA35 patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References:

1. Wang JL, Yang X, Xia K, Hu ZM, Weng L, Jin X, et al. TGM6 identified as a novel causative gene of spinocerebellar ataxias using exome sequencing. *Brain*. 2010;133(Pt 12):3510–8. [PubMed: 21106500]
2. Li M, Pang SY, Song Y, Kung MH, Ho SL, Sham PC. Whole exome sequencing identifies a novel mutation in the transglutaminase 6 gene for spinocerebellar ataxia in a Chinese family. *Clin Genet*. 2013;83(3):269–73. [PubMed: 22554020]
3. Folk JE. Mechanism and basis for specificity of transglutaminase-catalyzed epsilon-(gamma-glutamyl) lysine bond formation. *Adv Enzymol Relat Areas Mol Biol*. 1983;54:1–56. [PubMed: 6133417]
4. Stamnaes J, Dørum S, Fleckenstein B, Aeschlimann D, Sollid LM. Gluten T cell epitope targeting by TG3 and TG6; implications for dermatitis herpetiformis and gluten ataxia. *Amino Acids*. 2010;39(5):1183–91. [PubMed: 20300788]
5. Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, et al. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. *Lancet*. 1998;352(9140):1582–5. [PubMed: 9843103]
6. Hadjivassiliou M. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain*. 2003;126(3):685–91. [PubMed: 12566288]
7. Hadjivassiliou M, Davies-Jones GA, Sanders DS, Grunewald RA. Dietary treatment of gluten ataxia. *J Neurol Neurosurg Psychiatry*. 2003;74(9):1221–4. [PubMed: 12933922]
8. Hadjivassiliou M, Aeschlimann P, Sanders DS, Maki M, Kaukinen K, Grunewald RA, et al. Transglutaminase 6 antibodies in the diagnosis of gluten ataxia. *Neurology*. 2013;80(19):1740–5. [PubMed: 23576621]

9. Harding AE. The clinical features and classification of the late onset autosomal dominant cerebellar ataxias. A study of 11 families, including descendants of the 'the Drew family of Walworth'. *Brain*. 1982;105(Pt 1):1–28. [PubMed: 7066668]
10. Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroffe N, Aeschlimann D. Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. *Ann Neurol*. 2008;64(3):332–43. [PubMed: 18825674]
11. Boscolo S, Lorenzon A, Sblattero D, Florian F, Stebel M, Marzari R, et al. Anti transglutaminase antibodies cause ataxia in mice. *PLoS One*. 2010;5(3):e9698. [PubMed: 20300628]
12. Guo YC, Lin JJ, Liao YC, Tsai PC, Lee YC, Soong BW. Spinocerebellar ataxia 35: novel mutations in TGM6 with clinical and genetic characterization. *Neurology*. 2014;83(17):1554–61. [PubMed: 25253745]
13. Tripathy D, Vignoli B, Ramesh N, Polanco MJ, Coutelier M, Stephen CD, et al. Mutations in TGM6 induce the unfolded protein response in SCA35. *Hum Mol Genet*. 2017;26(19):3749–62. [PubMed: 28934387]
14. Yang ZH, Shi MM, Liu YT, Wang YL, Luo HY, Wang ZL, et al. TGM6 gene mutations in undiagnosed cerebellar ataxia patients. *Parkinsonism Relat Disord*. 2018;46:84–6. [PubMed: 28927799]
15. Guan WJ, Wang JL, Liu YT, Ma YT, Zhou Y, Jiang H, et al. Spinocerebellar ataxia type 35 (SCA35)-associated transglutaminase 6 mutants sensitize cells to apoptosis. *Biochem Biophys Res Commun*. 2013;430(2):780–6. [PubMed: 23206699]

Figure 1:

Four-generation pedigree. The arrow indicates the proband. Age of proband's siblings, III-1: 65, III-2: 64, proband (III-3): 63 and III-4: 60. III-1 and III-2 have symptoms onset in their late 30's. Clinical information for generation I is not available.

Table. 1:

SARA scores from multiple visits.

	Initial visit Month -7	Month -4	Start of gluten-free diet	Month +5	Month +8	Month+15
Gait	4	5	5	6	6	6
Stance	4	2	2	3	3	3
Sitting	1	0	0	0	0	0
Speech	2	3	3	2	2	2
Finger chase	2	2	2.5	2	2	1.5
Nose-to-finger	2	3	2	1	1	1
FAM	3	2	3	3	2	3
HSS	3	3	3	1	3	2
Total score	21	20	20.5	18	19	18.5

Time is in reference to the initiation of gluten-free diet.

FAM: fast alternating hand movements. HSS: heel-shin slide.

Table. 2:Mutations of *TGM6* reported in SCA35 patients.

Mutation	Exon/Intron	Protein	Type of mutation	TG6 activity	Ethnicity	<i>n</i>	Reference
c.1550T>G	Exon 10	L517W	Missense	Reduced	Chinese	9	[1]
c.980A>G	Exon 7	D327G	Missense	Reduced	Chinese	2	[1]
				NS	Han-	2	[2]
c.1528G>C	Exon 10	D510H	Missense		Chinese		
				Reduced	Han-	2	[12]
c331C>T	Exon 3	R111C	Missense		Chinese		
			Deletion of	Reduced	Han-	1	[12]
c.1722_1724delAGA	Exon 11	E574del	Glu		Chinese		
c.543G>T	Exon 4	Q181H	Missense	Reduced	NA	1	[13]
c.H71G>A	Exon 9	V391M	Missense	Reduced	Asian	1	[13]
c.1322A>G	Exon 9	Y441C	Missense	Reduced	European	1	[13]
c.1342C>T	Exon 9	R448W	Missense	NS	Mixed	1	[13]
c.1505T>A	Exon 10	L502Q	Missense	NS	European	2 ^a	[13]
			Duplication	NS	European	2 ^a	[13]
c.1951_1952insAAC	Exon 12	Q652dup	of Gin				
			Splice-site	NA	Han-	2	[14]
c.7+1G>T	Intron 1	Splicing abnormality	mutation		Chinese		
				NA	Han-	1	[14]
c.1478C>T	Exon 10	P493L	Missense		Chinese		
c.841delG	Exon 6	Truncated protein	Frameshift mutation	Predicted to be reduced	Hispanic	1	This study

n, number of patients reported in the corresponding reference. NS: not significantly reduced. NA: not available.^aOne patient carries both L502Q and Q652dup [13] was counted in both rows.