JMD
https://doi.org/10.14802/jmd.16044 / J Mov Disord 2017;10(1):53-58
pISSN 2005-940X / eISSN 2093-4939

CASE REPORT

Familiar Hyperekplexia, a Potential Cause of Cautious Gait: A New Korean Case and a Systematic Review of Phenotypes

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ABSTRACT

Familial hyperekplexia, also called startle disease, is a rare neurological disorder characterized by excessive startle responses to noise or touch. It can be associated with serious injury from frequent falls, apnea spells, and aspiration pneumonia. Familial hyperekplexia has a heterogeneous genetic background with several identified causative genes; it demonstrates both dominant and recessive inheritance in the α1 subunit of the glycine receptor (*GLRA1*), the β subunit of the glycine receptor and the presynaptic sodium and chloride-dependent glycine transporter 2 genes. Clonazepam is an effective medical treatment for hyperekplexia. Here, we report genetically confirmed familial hyperekplexia patients presenting early adult cautious gait. Additionally, we review clinical features, mode of inheritance, ethnicity and the types and locations of mutations of previously reported hyperekplexia cases with a *GLRA1* gene mutation.

Key Words Hyperekplexia; *GLRA1*; deep phenotyping.

Hyperekplexia, or startle disease, is an uncommon nonepileptic disorder classically characterized by exaggerated startle responses to unexpected stimuli. It can occur as a hereditary disorder and is typically caused by a mutation in the alpha 1 subunit of the glycine receptor (*GLRA1*) gene.[1] The major form of hyperekplexia refers to the type that occurs in neonates, who have hypertonia or stiffness that tends to resolve over time.[2] We report a new case of genetically confirmed familial hyperekplexia caused by *GLRA1* mutation and systematically review the phenotypes reported in the literature.

CASE REPORT

A 20-year-old woman visited the neurology clinic for generalized stiffness and frequent falling episodes secondary to tactile stimuli. She was born at term, and her antenatal and birth history were not remarkable. There was no developmental delay or neurologic deficit; however, her parents had noticed sudden falling events since she was five years old. In response to unexpected tactile stimulation, she felt her body become rigid for a few seconds, which resulted in injurious falling down events with spared consciousness. She usually kept indoors and walked cautiously in order to avoid unexpected falling accidents. In childhood, the frequency of her falls was approximately four or five times per year, but after her teenage years, the frequency decreased to once or twice per year. She remembered that drinking alcohol ameliorated the symptoms. Her father and older sister had similar symptoms (Figure 1A). On physical examination, she had numerous scars on her forehead from previous falling accidents. Apart from cautious gait, her neurological examination was normal. Brain MRI and EEG were not remarkable.

Received: September 22, 2016 **Revised:** November 3, 2016 **Accepted:** November 4, 2016
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J Mov Disord 2017;10(1):53-58

Whole exome sequencing with genomic DNA extracted from peripheral blood identified a heterozygous missense mutation c.896G>A (reference sequence: NM_001146040.1) in *GLRA1*. No mutations were found in other genes known to cause familial hyperekplexia, such as *GLRB*, *SLC6A5*, *GPHN*,

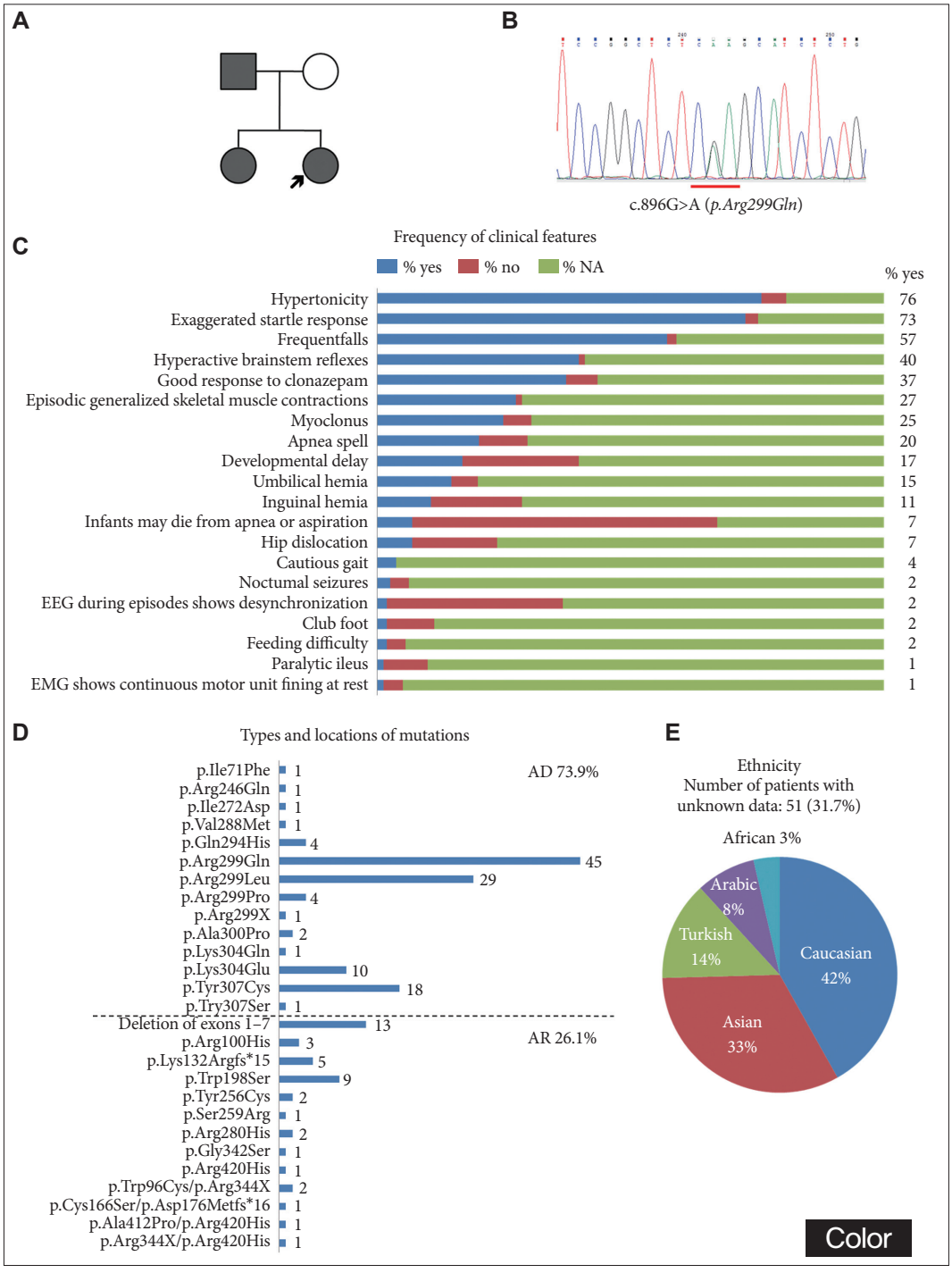

Figure 1. A pedigree of a Korean family with hyperekplexia (A). An arrow indicates the proband. Selected sequences from *GLRA1* exon 7 indicating the c.896G>A mutation using reverse primers (B). The results of systematic review of the literature regarding hyperekplexia caused by *GLRA1* mutation are shown with respect to percentage of clinical features (C) and types and locations of mutations with mode of inheritance (D) and ethnicity (E). In the percentage bar graph (C), blue refers to present, red refers to absent, and green means not available. Numbers beside the bars in graph D represent number of cases with the specified mutation. NA: not available, AD: autosomal dominant, AR: autosomal recessive.

and *ARHGEF9*. The change in the patient's *GLRA1* sequence alters the arginine codon at 299 to a glycine codon (p.Arg299Gln). This mutation was confirmed by Sanger sequencing (Figure 1B). The same mutation was also found in her sister, who was symptomatic; however, we could not perform a genetic study on her parents. Clonazepam was administered at a dose of 0.5 mg per day, which resulted in an improvement in the startle response.

DISCUSSION

Hyperekplexia, known as a hereditary startle disease, is characterized by an exaggerated startle response and neonatal hypertonia. This disorder is a rare neurogenetic condition, but it is potentially treatable.[1] The symptom spectrum can vary from an exaggerated startle response to infantile apnea spells and even injurious falls. The disease can be accompanied by abdominal hernia, hip dislocation and developmental delay.[2] A previous case study reported a possible association with sudden infant death syndrome.[3] In patients with hyperekplexia, no abnormalities are observed on routine blood tests, urinalysis, brain imaging studies, or EEG.[1] Hyperekplexia could be misdiagnosed as epilepsy, cerebral palsy, anxiety disorder, or conversion disorder and therefore can be mistreated. Early diagnosis and treatment are important, as they not only prevent injuries but may also influence the quality of life of a patient.

To conduct a systematic review of the literature regarding hyperekplexia cases caused by mutation in the *GLRA1* gene, we retrieved articles from the PubMed database using the keywords "Hyperekplexia AND *GLRA1*, English" and "Hyperekplexia AND case, English". The references used in this systematic review are listed in the supplementary information. Clinical features, ethnicity, types and locations of mutations and mode of inheritance, as obtained from the retrieved literature, are summarized in Table 1. Most patients showed neonatal hypertonia (76%) and an exaggerated startle response (73%). Most patients (64 out of 66 cases with the nose-tapping test) exhibited a hyperactive brainstem reflex, which was found with the nose-tapping test. Exaggerated head retraction reflexes in response to the nose-tapping test indicate exaggerated brainstem reflexes and provide an important clue to diagnose hyperekplexia. The patients also suffered from severe complications, such as developmental delay (16.8%) and apnea spells (20.7%). External abnormalities, such as umbilical (13.9%) and inguinal hernia (11.2%), hip dislocation (6.8%) and club foot (1.9%), were not uncommonly observed (Figure 1C). These findings are consistent with a previous case series that is not included in our analysis.[4] Clinical features that helped differentiate hyperekplexia from epilepsy included unexpected stimulus-inducing falling accidents, short episodes lasting only a few seconds, and spared consciousness, with no other abnormal movements accompanying the event. Cautious gait, face lacerations and family history may be helpful for differentiating hyperekplexia from conversion disorder. Frequent falls were observed in 39.8% of cases for which information was available, and cautious gait was reported infrequently (4%). Data regarding falls and gait might have been biased by patients' age, and therefore, there is a potential for missed information. Six out of 161 reviewed patients exhibited a wide-based and stiff gait due to considerable fear of an unexpected falling event, and two patients lacked confidence in outdoor environments, resulting in impaired social behavior. Presentation of a cautious gait resulting from unexpected falling episodes might be an indication of hyperekplexia. Clonazepam, which enhances GABA-gated chloride channel function and presumably compensates for defective glycine-gated chloride channel function, has been considered the first choice for the treatment of hyperekplexia. Antiepileptic drugs, including carbamazepine, phenytoin, valproate, and vigabatrin, have also been used for treatment.[1] In this review, 60 out of 70 cases (85.7%) showed good response to clonazepam, which is similar to a previous study.[4]

Among genes causing familial hyperekplexia, *GLRA1* is the most common causative gene, accounting for 80% of hereditary cases.[5,6] Our patients carried a heterozygous mutation, p.Arg299Gln, which was inherited in an autosomal dominant fashion. Missense mutation of the arginine at codon 299, which was previously reported as codon 271, is the most common (Table 1, Figure 1D). Both autosomal dominant and recessive inheritance have been reported in familial hyperekplexia caused by *GLRA1* mutation. Our analysis showed that dominant inheritance (73.9%) was 3-fold more common-

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Table 1. Overview of included studies for hyperekplexia related mutation in *GLRA1* gene

Studies (years)	Study design	*n* cases	Male (%)	*n* of family and case	Mode of inheritance	Ethnicities	Age of onset	Symtpoms	Reported mutations	Mutation position according to NP_000162
Present family	Family study	3	33	1	AD	Asian	C	SR (2), FI, NT	p.Arg271n	p.Arg299Gln
Mine et al. (2015)	Original article	16*	50	11	AD (14), AR (2)	Asian	I	NH, SR, AS (few), DD (1), NT, UH (10)	p.Arg271Gln (10) p.Ala272Pro (2) p.Tyr279Cys (1) p.Lys276Glu (1) p.Ala384Pro/p.Arg392His (1) p.Arg316X/p.Arg392His (1)	p.Arg299Gln p.Ala300Pro p.Tyr307Cys p.Lys304Glu p.Ala412Pro/p.Arg420His p.Arg344X/p.Arg420His
Hmami et al. (2014)	Case report/ series	1	100	1‡	AR	African	I	NH, SR, AS, NT	p. Arg392His	p. Arg420His
Horváth et al. (2014)	Case report/ series	1	100	1	AD	Asian	I	NH, HD	p.Ile43e	p.Ile71Phe
Lee et al. (2013)	Original article	1*	100	1	AD	Asian	I	NH, SR, FD	p.Arg271	p.Arg299X
Chan et al. (2014)	Case report/ series	1	100	1	AR	Asian	I	SR, Rg, FI, DD, NT	p.Cys138Ser/ p.Asp148Metfs*16	p.Cys166Ser/ p.Asp176Metfs*16
Zoons et al. (2012)	Family study	5	20	1	AD	Caucasian	I (1), U (4)	NH (4), SR (4), FI (4), DM (4), NT	p.Lys104Argfs*15	p.Lys132Argfs*15
Al-Futaisi et al. (2012)	Family study	9	78	2‡	AR	Arabic	I (6), C (3)	NH (6), SR (9), AS (1), DD (8), NT (1)	p.Trp170Ser	p.Trp198Ser
Gregory et al. (2008)	Family study	4	50	1‡	AD	African	I (2), C (2)	NH (2), SR (3), AS (1), FD (1), DD (2), UH (2)	p.Arg271Pro	p.Arg299Pro
Kang et al. (2008)	Case report/ series	1	100	1	AD	Asian	I	NH, SR, DM, NT	p.Lys276Gln	p.Lys304Gln
Forsyth et al. (2007)	Case report/ series	2	0	1‡	AR	Turkish	I	NH (1), SR, Rg (1), FI (1), AS (1), DD, NT	p.Tyr228Cys	p.Tyr256Cys
Doria Lamba et al. (2007)	Family study	7	71	1	AD	Unknown	I	NH, SR, FI (6), AS (4), DM, NT, UH	p.Lys276Glu	p.Lys304Glu
Becker et al. (2006)	Family study	7	83	6‡	AR	Turkish	I	NH, SR, FI (1), AS (2), DM (1), NT (1)	deletion of exons 1–7	deletion of exons 1–8
Sirén et al. (2006)	Family study	5	20	1‡	AR	Turkish	I	NH (3), SR (1), Rg (1), FI (3), AS, DD(1), NT (1)	deletion of exons 1–7	deletion of exons 1–8
Poon et al. (2006)	Case report/ series	1	0	1	AD	Asian	I	NH, SR	p.Tyr279Ser:het	p.Tyr307Ser:het

Table 1. Overview of included studies for hyperekplexia related mutation in *GLRA1* gene (continued)

Studies (years)	Study design	*n* cases	Male (%)	*n* of family and case	Mode of inheritance	Ethnicities	Age of onset	Symtpoms	Reported mutations	Mutation position according to NP_000162
Coto et al. (2005)	Family study	3	67	1	AR	Caucasian	I	NH, SR	p.Arg72His	p.Arg100His
Tsai et al. (2004)	Family study	2	0	1	AR	Asian	I (1), U (1)	SR, Rg, Fl, DD (1), NT (1)	p.Trp68Cys/p.Arg316X	p.Trp96Cys/p.Arg344X
Tijssen et al. (2003)	Original articles	6	67	6	AD	Caucasian	I	SR, Fl, NT, CF (2)	p.Arg271Gln (4) p.Lys276Glu (2)	p.Arg299Gln p.Lys304Glu
Miraglia Del Giudice et al. (2003)	Case report/ series	1	100	1	AD	Caucasian	I	NH, SR, Fl, AS, DD, DM, NT	p.Arg218Gln	p.Arg246Gln
Humeny et al. (2002)	Original articles	1	100	1‡	AR	Asian	I	SR, Fl, DD, NT	p.Ser231Arg	p.Ser259Arg
del Giudice et al. (2001)	Case report/ series	1	100	1	AD	Caucasian	I	NH, SR, Rg, NT	p.Val260Met	p.Val288Met
Kwok et al. (2001)	Case report/ series	3†	33	2	AD	Caucasian	I (2), U (1)	NH (2), SR, Fl, DD (1), NT (2)	p.Arg271Gln (1) p.Tyr279Cys (2)	p.Arg299Gln p.Tyr307Cys
Jungbluth et al. (2000)	Case report/ series	1	100		AD	Caucasian	I	NH, SR, Rg, Fl, DD, NT	p.Gly342Ser	p.Gly342Ser
Vergouwe et al. (1999)	Family study	2	50	1	AR	Caucasian	I	NH, SR, Fl, DD (1), NT, UH	p.Arg252His	p.Arg280His
Brune et al. (1996)	Original articles	1	0	1‡	AR	Turkish	I	NH, SR, AS, DD	Deletion of exons 1–6	Deletion of exon 1–7
Milani et al. (1996)	Family study	4	25	1	AD	Caucasian	I (1), U (3)	NH (2), SR (2), AS (1)	p.Gln266His	p.Gln294His
Rees et al. (1994)	Case report/ series	10	100	2	AD	Caucasian	I (9), U (1)	NH, SR, Rg, Fl, DM, UH (most)	p.Arg271Gln p.Ile244Asp	p.Arg299Gln p.Ile272Asp
Ryan et al. (1992)	Family study	29	41	1	AD	unknown	I	NH, AS (5), Fl (25), FD (1), DD (1), NT (1), IH (1)	p.Arg271leu	p.Arg299leu
Hayashi et al. (1991)	Family study	9	67	2	AD	Asian	I (7), U (2)	NH (5), SR (6), AS (4), Fl (8), NT (7), IH (2), HD (2)	p.Arg271Gln	p.Arg299Gln
Kurczynski (1983)	Family study	9	56	1	AD	Caucasian	I	NH (9), SR (8), AS (1), Fl (8), NT (3), UH (1)	p.Arg271Gln	p.Arg299Gln
Morley et al. (1982)	Family study	15	33	1	AD	Unknown	I	NH (12), SR, Fl, NT (2) IH (3), HD (6)	p.Tyr279Cys	p.Tyr307Cys

References of individual studies are summarized in Supplementary Material. *who had mutation in *GLRA1* gene, †whose clinical data was descripted in detail, ‡consanguineous marriage. AD: autosomal dominant, AR: autosomal recessive, I: infant, C: childhood, U: unknown, NH: neonatal hypertonia, SR: exaggerated startle response, Rg: rigidity, Fl: falling attack, AS: apnea spells, FD: feeding difficulty, DD: developmental delay, DM: diurnal myoclonus, NT: nose tapping test, UH: umbilical hernia, HD: hip dislocation, IH: inguinal hernia, CF: club foot.

ly reported than recessive inheritance (26.1%). Interestingly, most dominantly inherited mutations were located between codons 290–300 of the *GLRA1* gene (Figure 1D). Distribution of ethnicity in the reviewed hyperekplexia cases was Caucasian (42%), Asian (33%), Turkish (14%), Arabic (8%), and African (3%) (Figure 1E). In a genotype-ethnicity correlation, 8 Asian families (including isolated cases) and 7 Caucasian families demonstrated the p.Arg-299Gln mutation of the *GLRA1* gene. These findings support the notion that the Arg299 amino acid site is vulnerable to hyperekplexia in ethnically disparate cases.[7]

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.16044.

Conflicts of Interest

The authors have no financial conflicts of interest.

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