·Letter to the Editor·

A novel nonsense mutation of GPR143 gene in a Korean kindred with X-linked congenital nystagmus

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Dear Editor,

I am Dr. Ungsoo Samuel Kim, from Kim's Eye Hospital, Konyang University, Seoul, Korea. I write to present a novel mutation of GPR143 in Korean patients with X-linked congenital nystagmus by using exome sequencing.

Congenital nystagmus is an inherited ocular disorder that can occur as an X-linked condition. Three genetic loci have been identified for X-linked congenital nystagmus (XLCN): FERM domain containing 7 (FRMD7) at Xq26.2, G protein-coupled receptor 143 (GPR143) at Xp22.3, and NYS1 at Xp11.4-p11.3 [1-3]. Recently, calcium/calmodulin-dependent serine protein kinase (CASK) gene has also been identified as one of the genes that may be responsible for X-linked nystagmus with mental retardation[4]. The GPR143 gene, also known as OA1, has nine exons and encodes a 439-KD protein consisting of 404 amino acids that encode seven transmembrane segments, and shows homology to G protein-coupled receptors[5].

To date, more than 90 different GPR143 mutations have been reported. Among these, the mutations p.S89F, a 37-bp deletion at position 222 of the cDNA, c.849delT, c. 238_240delCTC, c.658+1G>A, c.353G>A, g. 1103_7266del6164, and 25985_26546del562 are the most common[3,6]. We have identified a novel mutation of GPR143 in Korean patients with XLCN by using exome sequencing.

A 63-year-old man complained of abnormal ocular movement and visual disturbances. Nystagmus was present from birth and strabismus surgery had been performed 20y before for exotropia without head nodding. We performed a full ophthalmologic examination including manifest refraction, slit-lamp examination, and fundus examination. Cover tests showed orthotropia and duction was normal. Spectral domain optical coherence tomography (Heidelberg Spectralis OCT, Heidelberg, Germany) was performed to investigate foveal hypoplasia. Nystagmus was evaluated using video nystagmography (SVNG, SLMED, Korea). The patient's family history revealed that three brothers and two maternal uncles had the same condition (Figure 1).

We prepared indexed, paired-end libraries, which were then enriched using the Trusight One sequencing panel (Illumina, USA) that covers 12 Mb of genomic DNA, including 4813 genes that have been associated with a clinical phenotype. Prepared libraries were loaded on to a flow cell and sequenced using a Miseq sequencer (Illumina, USA), with sequence data exported as a vcf file. Initially we focused on the identification of nonsynonymous variants, including splice acceptor and donor site mutations and insertions and deletions (indels) affecting coding regions, on the basis that synonymous variants were far less likely to be pathogenic.

The patient's best corrected visual acuity was 0.3 in both eyes using Snellen chart. Park and Oh [7] reported that the mean logMAR visual acuity of the patients with foveal hypoplasia was 0.57-0.58. The iris had slight hypopigmentation in the peripheral area (Figure 2A). Fundus examination showed a decreased foveal reflex and normal retinal vessels (Figure 2B). Spectral domain optical

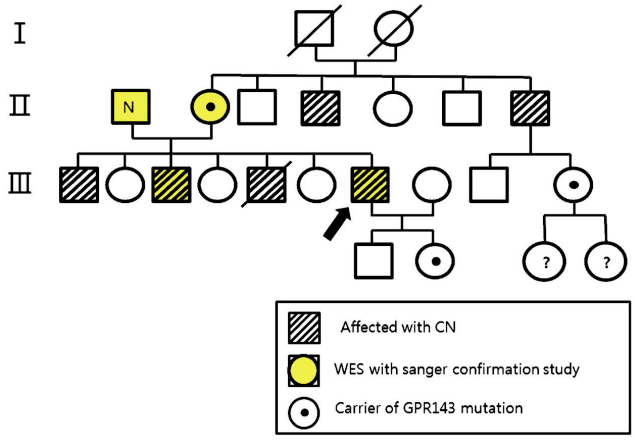

Figure 1 Pedigree structure CN: Congenital nystagmus; WES: Whole exome sequencing.

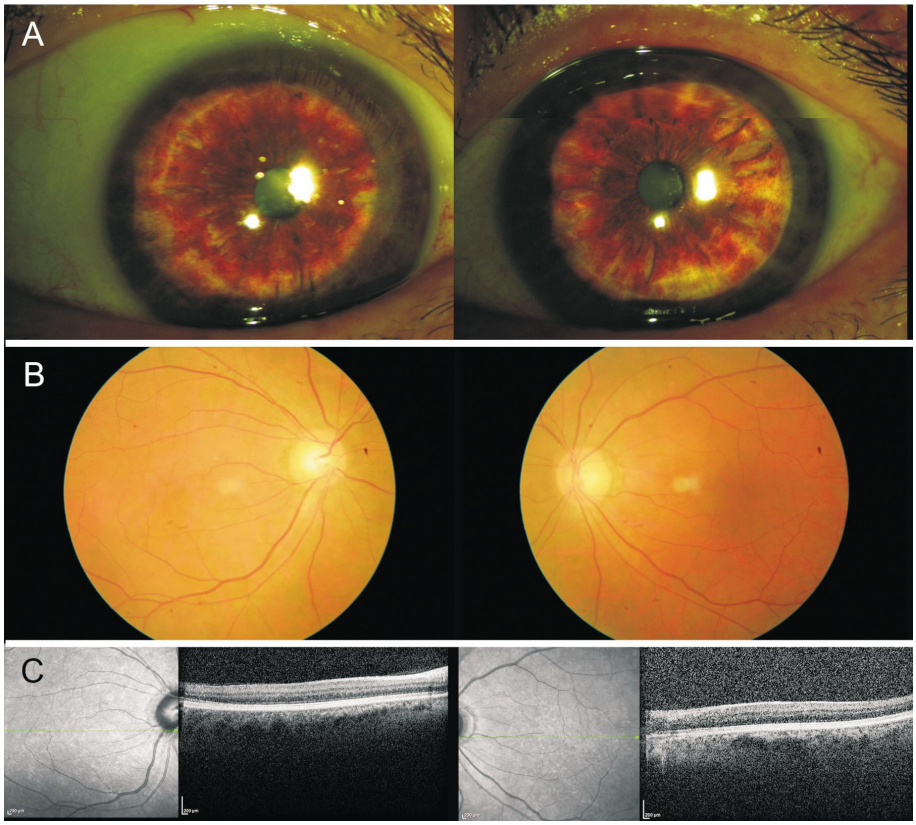

Figure 2 Ophthalmologic examinations of the patient A: Slit-lamp examination; B: Fundus photography; C: Spectral domain optical coherence tomography.

coherence tomography revealed foveal hypoplasia with a normal inner segment/outer segment junction of the photoreceptors in both eyes (Figure 2C). Jerky horizontal conjugate nystagmus (approximately 120 Hz) was noted on video nystagmography with increased amplitude of nystagmus in the left eye (Figure 3). Exome sequencing analysis detected the same hemizygous nonsense mutation (c.733C>T; encoding p. Arg245Ter) of the GPR143 gene, located on the X chromosome, in both brothers (Figure 4). The presence of this mutation in both brothers and their mother was confirmed by Sanger sequencing.

Mutations associated with XLCN have been reported at three loci (FRMD7, NYS1, and GPR143). We detected the same hemizygous nonsense mutation (c.733C>T; encoding p. Arg245Ter) in the GPR143 gene in an X-linked nystagmus patients using EXOME sequencing. This is the first report of Exome sequencing in X-linked nystagmus in Korean patients.

The GPR143 gene codes for a protein that is involved in pigmentation of the eye, especially the retinal epithelium and skin, through a signaling pathway that controls the growth and maturation of melanosomes. Foveal hypoplasia can be due to thickening of the photoreceptor layer; intact foveal anatomy appears to be related to physiological macular pigment storage in the neurosensory retina [8]. During development, cone cells undergo morphologic changes including thinning and elongation, and centripetal migration[9]. These changes lead to the formation of a foveal pit and may be related to visual development [10]. Foveal hypoplasia has been reported to be associated with chromosomal abnormalities, microophthalmus, and aniridia, and as an isolated finding [11]. However, ocular albinism might be associated with another process that causes the persistence of multiple retinal layers normally absent in the fovea [12]. Further investigations of the mechanism underlying foveal hypoplasia in ocular albinism with X-linked nystagmus are required.

In many individuals with GPR143 mutations, nystagmus is found without hypopigmentation even when the GPR143 protein is truncated by almost 75%[6]. The present case had foveal hypoplasia, the same finding as that in patients with a splicing site GPR143 mutation (24422G>C)[13]. However, in a report by Peng *et al* [14], all X-linked nystagmus patients with GPR143 duplication had normal fundi. Thus, the mutation locus or size may have an effect on pigmentation of the fovea.

Patients with ocular albinism and the absence of foveal pits can present without nystagmus [15]. Unfortunately, there have been few reports that have examined the relationship between the characteristics of nystagmus in the X-linked condition with the type of mutation involved. Yan *et al*[16] have reported that patients with GPR143 mutations had conjugate horizontal nystagmus. Peng *et al* [14] reported that a Chinese patient with XLCN caused by a 19-bp duplication in

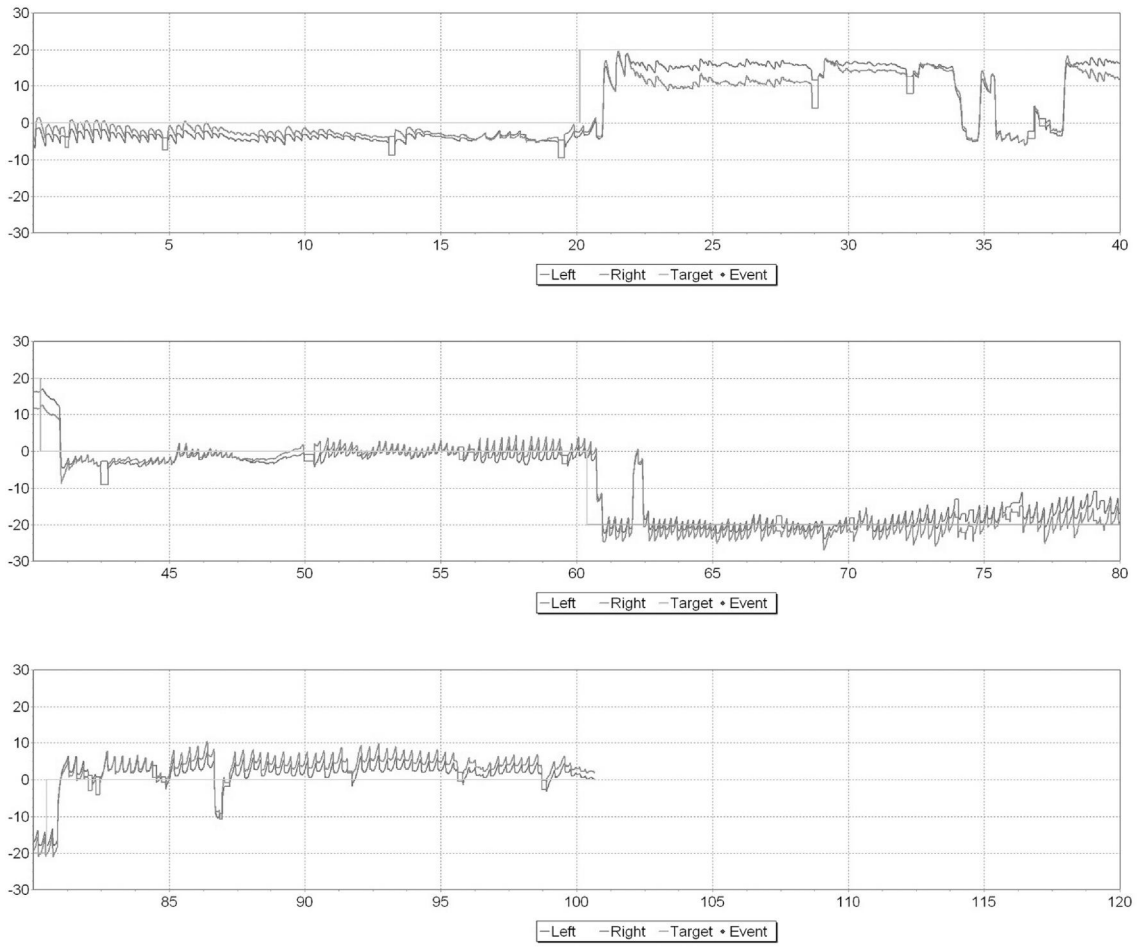

Figure 3 Video nystagmographic findings The amplitude of nystagmus increases in the left gaze direction.

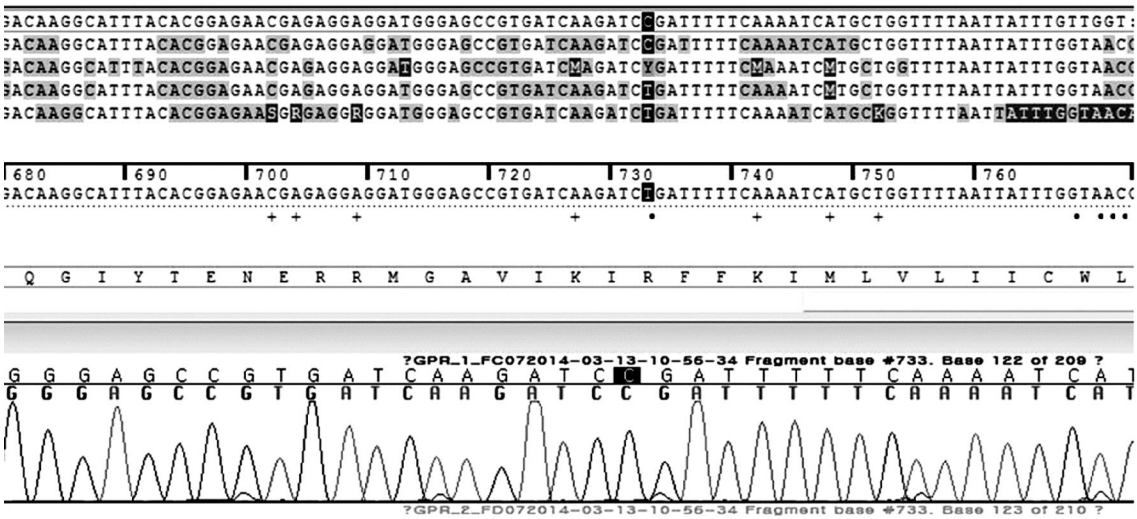

Figure 4 Identification of a novel mutation c.733C>T, p. Arg245 in the GPR143 gene.

the GPR143 gene had binocular spontaneous horizontal oscillations with an intermediate frequency (<120 counts per minute) without head nodding. The patient in this report also had jerky conjugate horizontal nystagmus at null point with a frequency of approximately 120 Hz. Interestingly, a higher proportion of pendular waveform types has been observed in patients with mutations of the FRMD7 gene, compared with the more jerky waveforms observed in ocular albinism[17].

The purpose of genetic testing is to establish an accurate diagnosis of disorders. It has advantages such as early detection, prenatal diagnosis, providing information about prognosis, and the identification of the risks of developing the disorder in patients and family members at risk. In conclusion, we have discovered a novel GPR143 mutation in a Korean patient with X-linked nystagmus, which appears to show a recessive inheritance pattern. It provides the genetic information about Korean X-linked nystagmus with GPR143 mutation.

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