Molecular Vision 2023; 29:234-244 <http://www.molvis.org/molvis/v29/234>
Received 14 June 2022 | Accepted 25 October 2023 | Published 1 November 2023

GPR143 mutations in an X-linked infantile nystagmus syndrome cohort in Southeast China

Jingling Xu,[1,2,3] Yihan Zheng,[3] Lulu Cheng,[4] Huihui Sun,[5] Xinping Yu,[3] Feng Gu,[3] E Song[2]

[1]Department of Ophthalmology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China; [2]Department of Ophthalmology, Lixiang Eye Hospital of Soochow University, Suzhou, Jiangsu, China; [3]Eye Hospital of Wenzhou Medical University Wenzhou China; [4]Eye Department in People's Hospital of Longgang District, Shenzhen, China; [5]Eye Department of Children Hosptial in Hebei Province, Shijiazhuang, China

Purpose: Infantile nystagmus syndrome (INS), or congenital nystagmus (CN), refers to a group of ocular motor disorders characterized by rapid to-and-fro oscillations of the eyes. *GPR143* is the causative gene of ocular albinism type 1 (OA1), which is a special type of INS that manifests as reduced vision, nystagmus, and iris and fundus hypopigmentation. Here, we explored the genetic spectrum of INS and the genotype–phenotype correlation.
Methods: A total of 98 families with INS from Southeast China were recruited for this study. A sample from each participant was subjected to PCR-based DNA direct sequencing of *GPR143*. Varied bioinformatics analysis was subsequently used in a mutation assessment. All participants received detailed ophthalmic examinations.
Results: Genetic analysis identified 11 *GPR143* mutations in 11.2% (11/98) of the X-linked INS families. These included seven novel mutations (c.899 C>T, c.886–2 A>G, c.1A>G, c.633_643del CCTGTTCCAAA, c.162_198delCGCGGGCC CCGGGTCCCCCGCGACGTCCCCGCCGGCC, c.628C>A, and c.178_179insGGGTCCC) and four known mutations. Patients who carried a *GPR143* mutation were found to present a typical or atypical phenotype of OA1. All patients with *GPR143* mutations manifested foveal hypoplasia; thus, about 45.8% (11/24) of the families with total X-linked INS exhibited foveal hypoplasia.
Conclusions: We discovered seven novel mutations and four previously reported mutations of *GPR143* in a cohort of families with X-linked INS and enlarged the Chinese genetic spectrum of INS. These findings offer new insights for developing genetic screening strategies and shed light on the importance of conducting genetic analysis in confirming the clinical diagnosis in unresolved patients and atypical phenotypes.

Infantile nystagmus syndrome (INS), also known as congenital nystagmus (CN), is an oculomotor control disorder. INS is characterized by involuntary, periodic, rapid to-and-fro oscillations of the eyes. This disease appears at birth or develops after approximately 3–6 months. The prevalence of INS in the general population has been estimated to range from 0.03% to 0.24% [1,2]. Some patients develop abnormal head position (AHP) to reduce nystagmus and obtain better vision [2]. INS has been divided into two types: congenital motive nystagmus (CMN) or isolated nystagmus, and congenital sensory nystagmus (CSM). While CMN is not accompanied by ocular abnormalities, CSM is accompanied by other ocular disorders, including ocular albinism, congenital cataract, congenital corneal leukoma, strabismus, aniridia, achromatopsia, Leber congenital amaurosis, retinitis pigmentosa, cone–rod dystrophy, macular coloboma, and optic nerve hypoplasia [2,3]. According to the literature, there seems to be no cure for INS. Extraocular muscle surgery, optical therapy, and drug therapy have been used to improve visual acuity, reduce nystagmus, and correct AHP [4,5].

Various modes of inheritance of INS have been reported, including X-linked inheritance, autosomal dominant inheritance, and autosomal recessive inheritance [6]. The gene *GPR143*, also known as *OA1*, is one of the causative genes of X-linked INS. *GPR143* is located in Xp22.2 and encodes G protein-coupled receptor 143 (GPR143), which is the receptor for tyrosine, Levadopa, and dopamine. GPR143 is enriched in melanocytes and iris and retinal pigment epithelium and is involved in melanosome biogenesis, organization, and transport mechanisms. However, despite more than 100 mutations in *GPR143* being recorded in the human gene mutation database (HGMD), the pathogenic mechanism of *GPR143* has not been confirmed. It is known, however, that *GPR143* mutations cause ocular albinism type 1 (OA1), which is a special type of INS. People with OA1 exhibit reduced vision, nystagmus, foveal hypoplasia, iris hypopigmentation, and albinistic fundus. OA1 affects only the eyes; it does not affect the pigmentation of hair and skin. Iris hypopigmentation and albinistic fundus tend to be more atypical or mild in

Correspondence to: Song E, Department of Ophthalmology, Lixiang Eye Hospital of Soochow University, Number 192, Ganjiang East Road, Suzhou, Jiangsu Province, China; Phone: 0512-69359811; email: songe@suda.edu.cn

Chinese patients, and Chinese OA1 patients are often simply misdiagnosed with isolated nystagmus [7-11].

In this study, we aimed to explore the genetic spectrum of INS and the genotype–phenotype correlation. We enrolled 98 families from Southeast China who had been initially diagnosed with X-linked INS. We then performed Sanger sequencing of all coding exons and splicing sites of *GPR143*. A total of seven novel mutations and four known mutations of *GPR143* were found in 11 unrelated Chinese families.

METHODS

Ethics statement and study subjects: The study was approved by the review board of Wenzhou Medical University and was in accordance with the tenets of the Declaration of Helsinki. All participants and their parents received information about the study and signed an informed consent document before their enrollment in the study.

The patients participated in the study within the Strabismus and Amblyopia Clinic of the Eye Hospital of Wenzhou Medical University from 2014 to 2020. A total of 98 Chinese probands who were diagnosed with INS, as well as their parents, were recruited for this study. All the recruited patients were male. A group of 100 racially and geographically matched controls were also enrolled. All the recruited controls were free of other ocular diseases or systemic diseases. The medical records of those controls who had undergone surgery were excluded from our study.

Mutational screening and genetic analysis: Peripheral blood samples were collected and stored in a freezer at −20 °C. DNA was then extracted from peripheral blood lymphocytes using standard protocols (Roche Biochemical, Inc.). Genetic testing was performed in the Gene Correction and Stem Cells Laboratory of Wenzhou Medical University. The DNA sequences encoding GPR143 were obtained from the GenBank database (NM_000273.2). Primers were designed to cover all coding exons and splice junctions of GPR143 in the online program Exon Primer. Pathogenicity was evaluated using SIFT, Polyphen2 HDIV, Polyphen2 HVAR, Mutation Taster, and PROVEAN. Mutations with a minor allele frequency (MAF) were evaluated using the Genome Aggregation Database (gnomAD) and Exome Aggregation Consortium (EXAC). Co-segregation analysis was performed for mutations detected in patients and their parents.

Amino acid sequences were obtained from the National Center for Biotechnology Information. Multiple sequence alignments and the detection of conserved amino acid sequences were performed using Clustal Omega. The topological model of *GPR143* was predicted using SMART. Three-dimensional crystal structures of wildtype and mutant GPR143 were predicted using Phyre2 and visualized using PyMol software (Version 1.5; DeLano Scientific, San Carlos, CA).

Clinical examination: All patients underwent a detailed clinical examination. Ophthalmic examination included slit lamp examination, dilated fundus examination, ophthalmoscopic examination, and assessment of best corrected visual acuity (BCVA), refractive error, intraocular pressure, extraocular movements, and axial length using an IOLMaster, version 5.0 (Carl Zeiss Meditec, Jena, Germany). We used ultrahigh-resolution spectral-domain optical coherence tomography (SD-OCT; Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) to obtain tomograms from the affected family members.

RESULTS

Clinical features: In this study, we enrolled 98 families with X-linked INS. Among these 98 families, 24 families were found to have foveal hypoplasia, and 11.2% (11/98) of the families were found to carry GPR143 mutations (Figure 1). All patients with *GPR143* mutations showed foveal hypoplasia, accounting for 45.8% (11/24) of the families with X-linked INS with foveal hypoplasia.

The clinical characteristics of the probands who were found to be carrying GPR143 mutations are described in Table 1. All the probands were male and exhibited different degrees of horizontal nystagmus combined with refractive errors. Two patients (18.2%, 2/11) had affected esotropia, and two patients (18.2%, 2/11) had affected exotropia. Eight patients (72.7%, 8/11) had compensatory head positions. The BCVA of all patients was less than 0.3 (Snellen E chart). Five probands (45.5%, 5/11) presented with mild iris pigmentation. Nine probands (81.8%, 9/11) had mild to moderate degrees of fundus hypopigmentation, which allowed the visualization of the choroidal vessels (Figure 2). None of the patients in this study reported having abnormal skin and hair color.

Mutation analysis: Eleven mutations, including seven novel mutations and four previously reported mutations, were identified in 11 unrelated families (Figure 3). All the mutations were absent from the gnomAD.

The mutation c.886–2 A>G is a novel splicing mutation that occurs in the 3′ consensus acceptor region for the splicing of introns 8–9. This splicing mutation (c.886–2 A>G) was predicted to cause a loss of the original splicing site and further affect the normal structure and function of GPR143.

Two missense mutations, c.899 C>T p.P300L and c.628C>A p.P210T, were found in the transmembrane

domain of GPR143. The pathogenicity of the two variants was further verified using a range of bioinformatics tools (Table 2), and both were found to be evolutionarily conserved (Figure 4). The structural modeling of p.P300L and p.P210T in GRP143 showed significant structural alterations, which probably influenced the normal function of GPR143 (Figure 5). Another novel missense mutation, c.1A>G (p.M1V), was predicted to change the splice site and further affect the protein's features.

Three novel frameshift variants (c.178_179insGGGTCCC/P60Rfs*43, c.633_643del CCTGTTCCAAA/p.L212Dfs*10, and c.162_198delCGCGGGCCCCGGGTCCCCCGCGACGTCCCCGCCGGCC/p.A55Rfs20) in *GRP143* were also detected. These mutations all introduced a frameshift and a premature stop codon, truncating the protein in the fourth transmembrane domain, which would markedly influence the function of GRP143.

Four previously reported mutations (c.346T>C, c.488G>A, c.360+1G>C and c.733C>T) were uncovered in this study. The pathogenicity of the four previously reported variants was verified by multiple bioinformatics tools (Table 2).

Statistical analysis failed to identify any correlation between genotype (including the type and position of the mutation) and phenotype (including degree of retinal hypopigmentation and BCVA).

Localization of GPR143 mutations in the Chinese population: As a final step in this study, we analyzed the localization of *GPR143* splicing, missense, and nonsense mutations in Chinese OA1 patients. We included mutations reported previously and those identified in this study, and the results are shown in Figure 6. Interestingly, 88.9% of the mutations (24/27) were found to be located in or near the seven putative transmembrane domains of GPR143 [12].

DISCUSSION

A total of 98 families from Southeast China who had been initially diagnosed with X-linked INS were enrolled in this study. We identified seven novel mutations and four known mutations of *GPR143* in 11 unrelated families. The probands with mutations all exhibited nystagmus, foveal hypoplasia, reduced visual acuity (BCVA less than 0.4), and normal skin and hair color. Most (81.8%, 9/11) of the patients had different degrees of fundus hypopigmentation, and 45.5% (5/11) of the patients had mild degrees of iris hypopigmentation.

Clinical features of OA1 vary among different ethnic groups. The most prominent signs in Caucasian patients with OA1 are iris translucency, foveal hypoplasia, and fundus hypopigmentation [13-16]. African American males with OA1 have non-albinotic, moderately pigmented fundi, and no translucency of the iris [16]. Japanese patients have fundus hypopigmentation at a level between that of Caucasian and African American patients [17,18]. Therefore, it has been widely acknowledged that the level of ocular hypopigmentation is related to ethnic origin. Iris hypopigmentation and fundus hypopigmentation are usually mild in reported Chinese OA1 cases [19]. Due to the insidious and slight depigmentation of the iris and fundus, Chinese OA1 patients are prone to being misdiagnosed with isolated nystagmus.

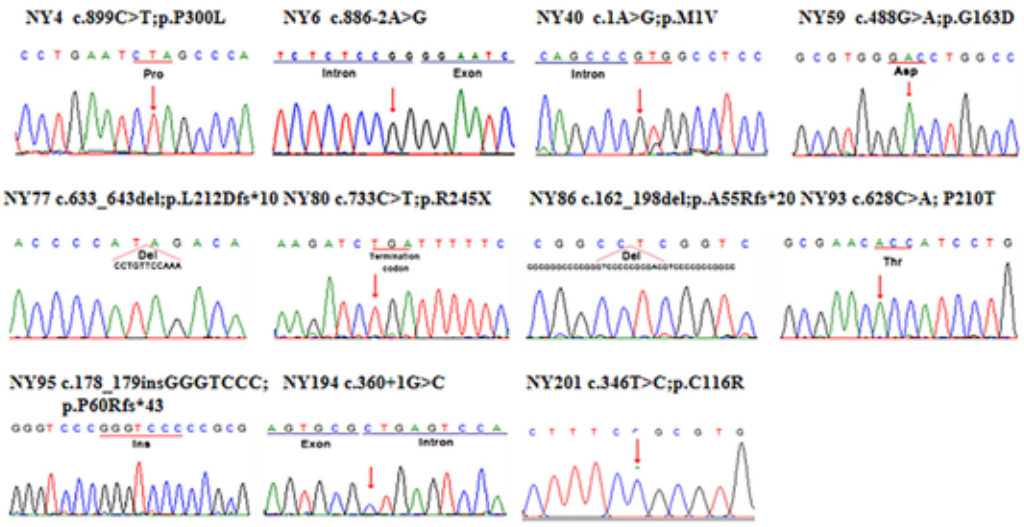

Figure 1. Potentially causative mutations identified in this study.

Table 1. Clinical features of families with *GPR143* mutations.

ID	Gender	Age	BCVA (OD/OS)	Refractive error	Strabismus	Iris hypopig-mentation	foveal hypoplasia	Nystagmus	Fundus hypopigmentation	AHP
NY4 IV1	M	6	0.2/0.2	OD:0/-2.00*180; OS:0/-2.00*180	N	N	Y	Horizontal jerk	Y	Y
NY6 II14	M	6	0.15/0.2	OD;+0.50/-1.00*10 OS:+0.50/-1.25*175	N	mild	Y	Horizontal pendular	Y	Y
NY40 IV3	M	5	0.2/0.2	OD:-1.00/-2.25*180; OS:0/-2.00*10	Exo10°	mild	Y	Horizontal pendular	Y	N
NY59 IV2	M	11	0.2/0.2	OD:+2.00/-2.00*180; OS:+2.00/-2.00*180	Eso20°	mild	Y	Horizontal pendular	Y	Y
NY77IV5	M	20	0.1/0.16	OD:+7.50/-2.50*140; OS:+7.50/-3.50*40	Eso 20°	N	Y	Horizontal jerk	Y	Y
NY80IV2	M	5	0.16/0.16	OD: +1.50 OS: +1.75/-1.00*20	N	N	Y	Horizontal pendular	N	NA
NY86 III3	M	14	0.2/0.16	OD:-9.00/-4.00*180 OS:-10.00/-4.00*180	N	N	Y	Horizontal jerk	Y	Y
NY93 IV3	M	8	0.2/0.2	OD:-1.00/-3.00*180 OS:-1.50/-2.50*175	N	N	Y	Horizontal jerk	N	Y
NY194 III1	M	7	0.1/0.1	OD:-3.00/-1.00*25 OS:-3.00/-0.50*10	No	mild	Y	Horizontal jerk	Y	Y
NY201IV6	M	7	0.2/0.3	OD:-1.25/-4.00*180 OS:-0.75/-4.50*180	Exo10°	mild	Y	Horizontal jerk	Y	Y
NY95IV4	M	3	0.2/0.2	OD: +2.50 OS: +2.75/-1.00*20	N	N	Y	Horizontal jerk	Y	NA

Y, present; N, absent; NA, not available; BCVA, best corrected vision acuity; Exo, exotropia; Eso, esotropia; OD, right eye; OS, left eye; AHP, abnormal head position

In this study, the GPR143 mutation detection rate was 11.22% (11/98). However, the mutation detection rate in families with foveal hypoplasia was significantly higher at 45.9% (11/24). Therefore, the application of genetic testing is crucial for the precise diagnosis of INS, especially in patients with foveal hypoplasia or cases of suspected clinical manifestations of albinism.

GPR143 consists of nine exons that span approximately 40 kb on chromosome Xp22.2, and it encodes a protein comprising 404 amino acids (Figure 6). GPR143 is expressed exclusively in melanosomes, a type of intracellular organelle, and is abundant in the retinal pigment epithelium (RPE) and melanocytes. However, the details of the molecular mechanism(s) associated with *GPR143* mutations that cause ocular abnormalities are still unclear. A hypothesis has been proposed that L-DOPA (a precursor in melanin synthesis) is a ligand of GPR143 in melanosomal biogenesis [20]. Mutations in *GPR143* could thus hinder melanin synthesis in the RPE and result in RPE hypopigmentation. This condition could then result in abnormal development of the retina and visual pathways, thereby causing nystagmus, misrouting of the optic fibers, foveal hypoplasia, and reduced visual acuity [7,21-24].

Three novel frameshift variants (c.178_179insGGGTCCC/P60Rfs*43, c.633_643del CCTGTTCCAAA, and c.162_198delCGCGGGCCCCGGGTCCCCCGCGACGTCCCCGCCGGCC) in *GRP143* were predicted to generate abnormal mRNA with a premature termination codon (PTC). These abnormal mRNAs with a PTC could be degraded under the nonsense-mediated mRNA decay (NMD) surveillance mechanism or generate defective truncated proteins that escape NMD surveillance.

A novel splicing mutation (c.886–2 A>G) was identified in the 3′ consensus acceptor region for the splicing of introns 8–9. Another novel mutation (c.1A>G) was predicted to alter the splice site. Such splice site displacement may result in short abnormal mRNA sequences and further generate

Figure 2. Images generated from the fundus camera and SD-OCT stack. Macular OCT images showing the fundus appearance in (**A**) patients with ocular albinism type 1 (OA1) and (**B**) healthy people.

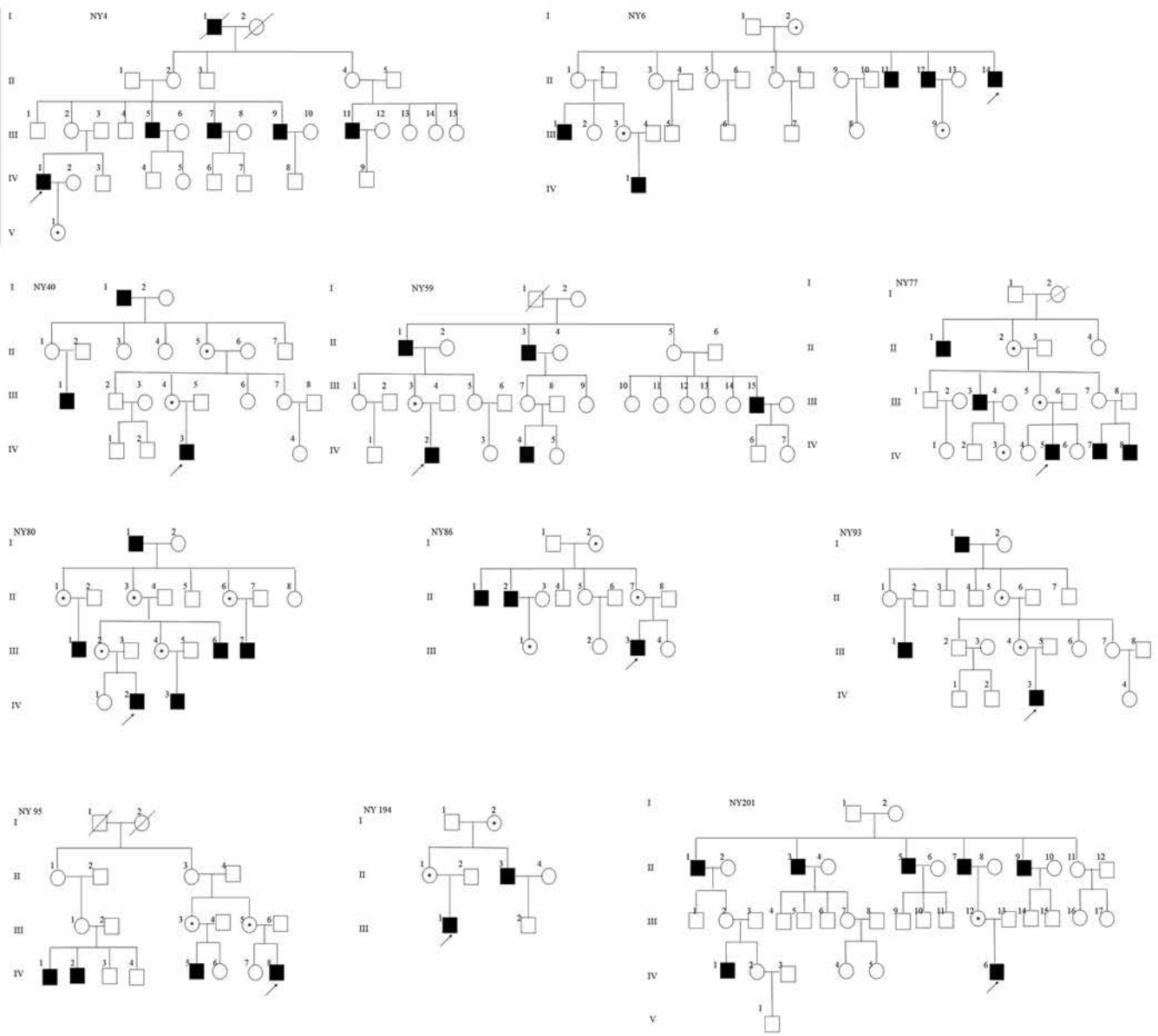

Figure 3. Pedigrees of the families in which infantile nystagmus syndrome (INS) was found to follow an X-linked mode of inheritance. Arrows indicate probands. Squares and circles represent males and females, respectively. Dotted circles show female carriers. Filled symbols represent affected patients.

truncated or nonfunctional proteins. In addition, two missense mutations (c.899 C>T/p.P300L and c.628C>A/p.P210T) were found for the first time in Southeast Chinese patients, and these mutations were also absent from the gnomAD. The crystal structure modeling of P300L and P210T in *GRP143* showed significant structural alterations in the presence of the mutations, which might affect the quantity and quality of melanin in the tissues.

Four previously reported mutations were also detected in families recruited for this study. To our knowledge, in this study, two known missense mutations (c.346T>C, p.C116R and c.488 G>A, p.G163D) were identified for the first time in Chinese INS patients. The splicing mutation c.360+1G>C has been reported previously in Chinese patients with X-linked ocular albinism [25]. The phenotype of Chinese patients carrying the mutation c.360+1G>C was similar, with low visual acuity, macular dysplasia, INS, and fundus depigmentation. The mutation c.733C>T was first reported in a Korean family with X-linked INS [26]. It was subsequently also found sporadically in Chinese patients [11] and in another

Table 2. Summary of the GPR143 mutations in our study.

Family	GPR143 mutation	Protein changes	Exon	Mutation type	GnomAD	SIFT	Mutation taster	Polyphen2 HDIV	Polyphen2 HVAR	PROVEAN
NY4	c.899 C>T	p.P300L	8	Missense	**N**	D(0.000)	DC(0.999)	PD(1)	PD(1)	D(−8.59)
NY6	c.886–2 A>G	-	8	Splicing	N		DC(1)			
NY40	c.1A>G	p.M1V	1	Missense	N	D(0.000)	DC(0.999)	PD(0.999)	PD(0.992)	D(−2.59)
NY59	c.488 G>A	p.G163D	4	Missense	N	D(0.012)	DC(0.999)	PD(1)	PD(0.999)	D(−3.74)
NY77	c.633_643del CCTGTTCCAAA;	p.L212Dfs*10	5	Frameshift	N		DC(1)	-		
NY80	c.733C>T	p.R245X	6	Nonsense	N	-	DC(1)	-	-	-
NY86	c.162_198del CGCGGGCCCC-GGGTCCCCCGCGAC-GTCCCCGCCGGCC	p.A55Rfs*20	1	Frameshift	N	-	DC(1)	-	-	-
NY93	c.628C>A;	p.P210T	5	Missense	N	D(0.000)	DC(0.999)	PD(0.999)	PD(0.981)	D(−7.64)
NY95	c.178_179insGGGTCCC	p.P60Rfs*43	1	Frameshift	N		DC(1)			
NY194	c.360+1G>C	-	2	Splicing	N		DC(1)			
NY201	c.346T>C	p.C116R	2	Missense	N	D(0.001)	DC(0.999)	PD(0.995)	PD(0.942)	D(−9.13)

DC, disease causing; D, deleterious; PD, probably damaging; N, absent

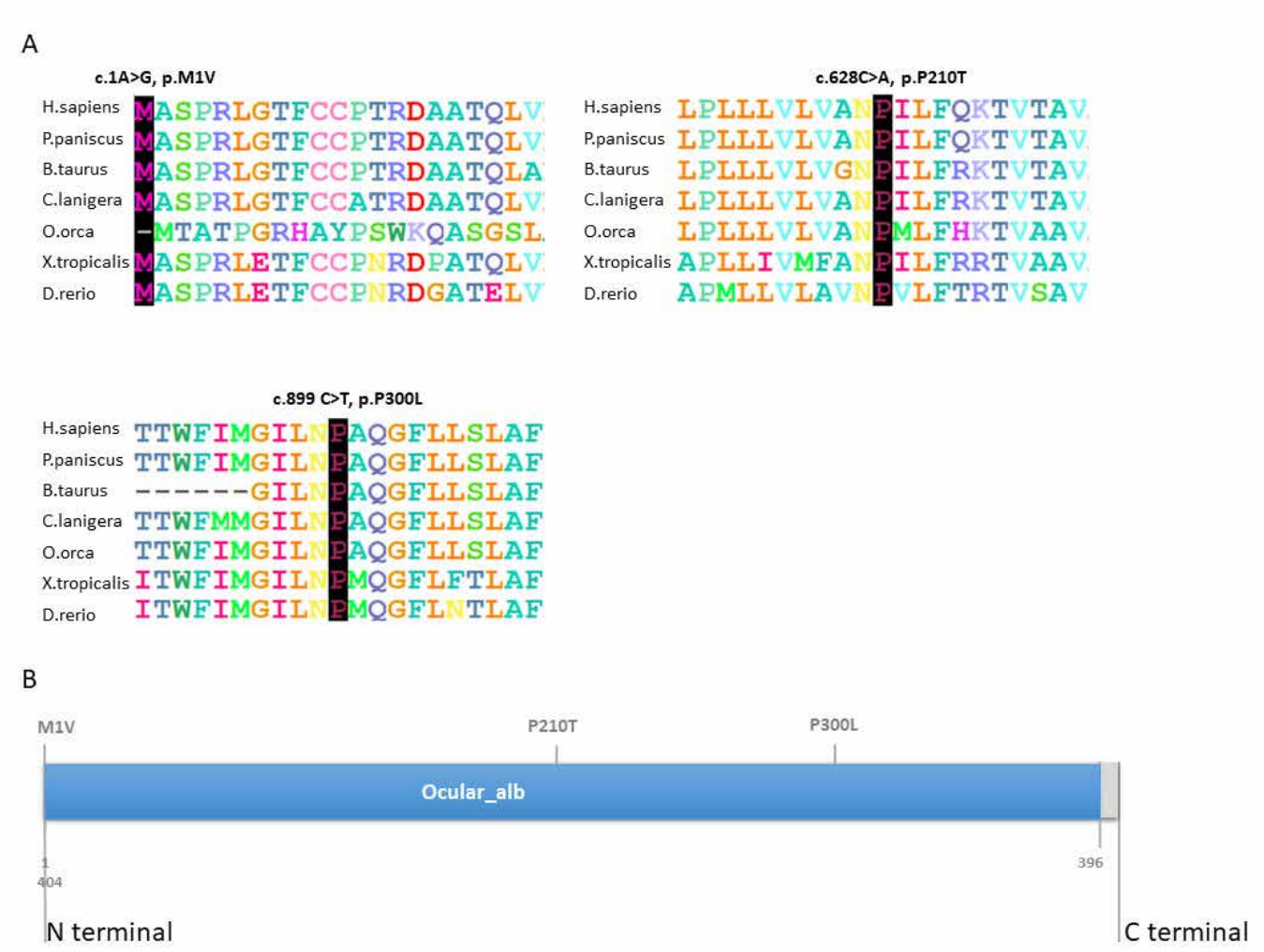

Figure 4. Mutational analysis of three novel missense mutations identified in *GPR143* gene. **A**: Evolutionarily conserved missense mutations of *GPR143*. **B**: Locations of identified missense mutations in *GPR143*.

unrelated Chinese family with X-linked INS [27]. The mutation c.733C>T is likely to be a hotspot mutation in Chinese and East Asian INS populations.

The characteristics of *GPR143* mutation sites found in the Chinese population were summarized for the first time in this study. Our findings show that up to 88.9% of identified mutations have been located in or near putative transmembrane domains. This finding suggests that the seven putative transmembrane domains of GPR143 are the most frequently mutated regions in Chinese OA1 patients and that the structural stability of the transmembrane domains is vital to the function of melanosomes.

In summary, we investigated 98 families from Southeast China with X-linked INS and identified 11 mutations in *GPR143*, including seven novel mutations and four previously described mutations. Identifying these mutations has deepened our understanding of the gene spectrum in patients in Southeast China. Genetic analysis can effectively improve the diagnostic accuracy of unresolved OA1 patients and atypical OA1 phenotypes. More effort should be put into elucidating the pathogenic mechanism of and possible gene therapies for nystagmus in the future.

ACKNOWLEDGMENTS

The authors thank Li Heming in helping to collect the patients. The authors appreciate the families who participated in this study. Supported by Innovative topics from Eye Hospital of Wenzhou Medical University (YNCX201309) and Jiangsu Distinguished Medical Experts Program (No.2016).

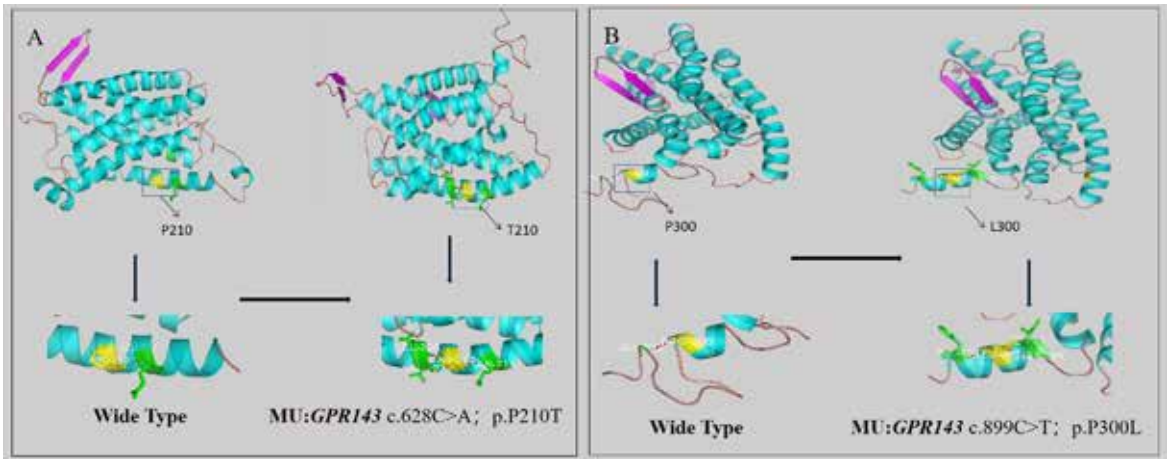

Figure 5. Simulated three-dimensional crystal structures of proteins. Predicted crystal structures of wildtype (left) and mutant (right) proteins. Yellow: wildtype (left) and mutant (right) residues. Green: residues that bind to wildtype (left) and mutant (right) residues.

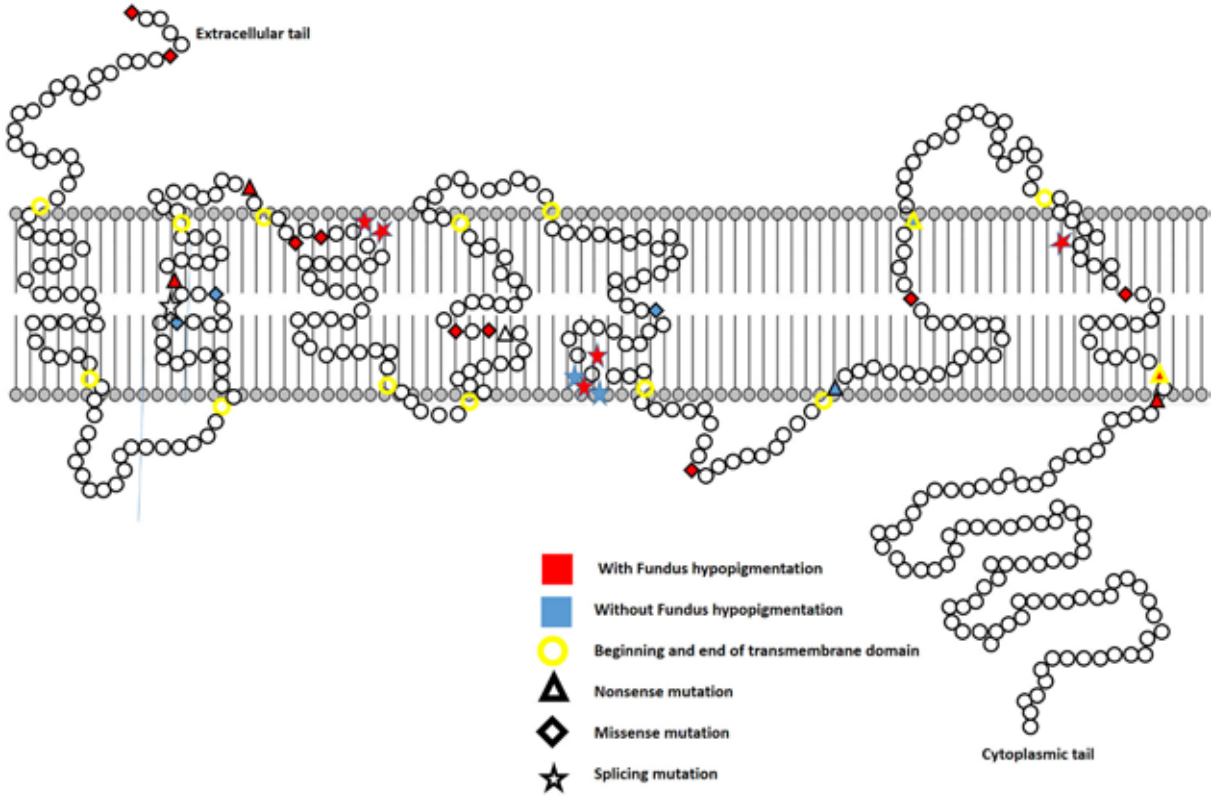

Figure 6. Protein model of GPR143 proposed by Ghosh et al. Splicing, missense, and nonsense mutations in GPR143 found in Chinese ocular albinism type 1 (OA1) patients (including mutations reported previously and those identified in this study) are indicated with colors and shapes. Triangles: missense mutations; rhombuses: missense mutations; star-marks: splice-site mutations; red: with fundus hypopigmentation; blue: without fundus hypopigmentation.

REFERENCES

1. Sarvananthan N, Surendran M, Roberts EO, Jain S, Thomas S, Shah N, Proudlock FA, Thompson JR, McLean RJ, Degg C, Woodruff G, Gottlob I. The prevalence of nystagmus: the Leicestershire nystagmus survey. Invest Ophthalmol Vis Sci 2009; 50:5201-6. [PMID: 19458336].
2. Watkins RJ, Thomas MG, Talbot CJ, Gottlob I, Shackleton S. The Role of FRMD7 in Idiopathic Infantile Nystagmus. J Ophthalmol 2012; 2012:460956[PMID: 21904664].
3. Richards MD, Wong A. Infantile nystagmus syndrome: clinical characteristics, current theories of pathogenesis, diagnosis, and management. Can J Ophthalmol 2015; 50:400-8. [PMID: 26651297].
4. Dell'Osso LF. Development of new treatments for congenital nystagmus. Ann N Y Acad Sci 2002; 956:361-79. [PMID: 11960819].
5. Hertle RW, Yang D, Adams K, Caterino R. Surgery for the treatment of vertical head posturing associated with infantile nystagmus syndrome: results in 24 patients. Clin Experiment Ophthalmol 2011; 39:37-46. [PMID: 20662845].
6. Bassi MT, Schiaffino MV, Renieri A, De Nigris F, Galli L, Bruttini M, Gebbia M, Bergen AA, Lewis RA, Ballabio A. Cloning of the gene for ocular albinism type 1 from the distal short arm of the X chromosome. Nat Genet 1995; 10:13-9. [PMID: 7647783].
7. Palmisano I, Bagnato P, Palmigiano A, Innamorati G, Rotondo G, Altimare D, Venturi C, Sviderskaya EV, Piccirillo R, Coppola M, Marigo V, Incerti B, Ballabio A, Surace EM, Tacchetti C, Bennett DC, Schiaffino MV. The ocular albinism type 1 protein, an intracellular G protein-coupled receptor, regulates melanosome transport in pigment cells. Hum Mol Genet 2008; 17:3487-501. [PMID: 18697795].
8. d'Addio M, Pizzigoni A, Bassi MT, Baschirotto C, Valetti C, Incerti B, Clementi M, De Luca M, Ballabio A, Schiaffino MV. Defective intracellular transport and processing of OA1 is a major cause of ocular albinism type 1. Hum Mol Genet 2000; 9:3011-8. [PMID: 11115845].
9. Liu JY, Ren X, Yang X, Guo T, Yao Q, Li L, Dai X, Zhang M, Wang L, Liu M, Wang QK. Identification of a novel GPR143 mutation in a large Chinese family with congenital nystagmus as the most prominent and consistent manifestation. J Hum Genet 2007; 52:565-70. [PMID: 17516023].
10. Gao X, Liu T, Cheng X, Dai A, Liu W, Li R, Zhang M. A novel GPR143 mutation in a Chinese family with X-linked ocular albinism type 1. Mol Med Rep 2020; 21:240-8. [PMID: 31746431].
11. Wang XF, Chen H, Huang PJ, Feng ZK, Hua ZQ, Feng X, Han F, Xu XT, Shen RJ, Li Y, Jin ZB, Yu HY. Genotype-Phenotype Analysis and Mutation Spectrum in a Cohort of Chinese Patients With Congenital Nystagmus. Front Cell Dev Biol 2021; 9:627295[PMID: 33732697].
12. Ghosh A, Sonavane U, Andhirka SK, Aradhyam GK, Joshi R. Structural insights into human GPCR protein OA1: a computational perspective. J Mol Model 2012; 18:2117-33. [PMID: 21938455].
13. Kinnear PE, Jay B, Witkop CJ Jr. Albinism. Surv Ophthalmol 1985; 30:75-101. [PMID: 3934778].
14. Charles SJ, Green JS, Grant JW, Yates JR, Moore AT. Clinical features of affected males with X linked ocular albinism. Br J Ophthalmol 1993; 77:222-7. [PMID: 8494858].
15. Schnur RE, Wick PA, Bailey C, Rebbeck T, Weleber RG, Wagstaff J, Grix AW, Pagon RA, Hockey A, Edwards MJ. Phenotypic variability in X-linked ocular albinism: relationship to linkage genotypes. Am J Hum Genet 1994; 55:484-96. [PMID: 7915878].
16. Oetting WS. New insights into ocular albinism type 1 (OA1): Mutations and polymorphisms of the OA1 gene. Hum Mutat 2002; 19:85-92. [PMID: 11793467].
17. Hayakawa M, Kanai A, Kato K, Nakajima A, Takamori K. A Japanese family of Nettleship Falls X-linked ocular albinism. Nippon Ganka Gakkai Zasshi 1990; 94:1181-7. [PMID: 2082739].
18. Shiono T, Tsunoda M, Chida Y, Nakazawa M, Tamai M. X linked ocular albinism in Japanese patients. Br J Ophthalmol 1995; 79:139-43. [PMID: 7696233].
19. Fang S, Guo X, Jia X, Xiao X, Li S, Zhang Q. Novel GPR143 mutations and clinical characteristics in six Chinese families with X-linked ocular albinism. Mol Vis 2008; 14:1974-82. [PMID: 18978956].
20. Ghosh A, Sonavane U, Andhirka SK, Aradhyam GK, Joshi R. Structural insights into human GPCR protein OA1: a computational perspective. J Mol Model 2012; 18:2117-33. [PMID: 21938455].
21. Schiaffino MV, d'Addio M, Alloni A, Baschirotto C, Valetti C, Cortese K, Puri C, Bassi MT, Colla C, De Luca M, Tacchetti C, Ballabio A. Ocular albinism: evidence for a defect in an intracellular signal transduction system. Nat Genet 1999; 23:108-12. [PMID: 10471510].
22. Young A, Jiang M, Wang Y, Ahmedli NB, Ramirez J, Reese BE, Birnbaumer L, Farber DB. Specific interaction of Galphai3 with the Oa1 G-protein coupled receptor controls the size and density of melanosomes in retinal pigment epithelium. PLoS One 2011; 6:e24376[PMID: 21931697].
23. De Filippo E, Schiedel AC, Manga P. Interaction between G Protein-Coupled Receptor 143 and Tyrosinase: Implications for Understanding Ocular Albinism Type 1. J Invest Dermatol 2017; 137:457-65. [PMID: 27720922].
24. Shen B, Samaraweera P, Rosenberg B, Orlow SJ. Ocular albinism type 1: more than meets the eye. Pigment Cell Res 2001; 14:243-8. [PMID: 11549106].
25. Schiaffino MV, Tacchetti C. The ocular albinism type 1 (OA1) protein and the evidence for an intracellular signal transduction system involved in melanosome biogenesis. Pigment Cell Res 2005; 18:227-33. [PMID: 16029416].
26. Han R, Wang X, Wang D, Wang L, Yuan Z, Ying M, Li N. GPR143 Gene Mutations in Five Chinese Families with

X-linked Congenital Nystagmus. Sci Rep 2015; 5:12031-[PMID: 26160353].

27. Kim US, Cho E, Kim HJ. A novel nonsense mutation of GPR143 gene in a Korean kindred with X-linked congenital nystagmus. Int J Ophthalmol 2016; 9:1367-70. [PMID: 27672609].

28. Jiang J, Yang L, Li H, Huang L, Li N. Evaluation of the iris thickness changes for the Chinese families with GPR143 gene mutations. Exp Eye Res 2019; 189:107819[PMID: 31574285].

Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 1 November 2023. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.