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A NOVEL VARIANT OF THE *GPR143* GENE CAUSES CONGENITAL NYSTAGMUS AND OCULAR ALBINISM IN A VIETNAMESE FAMILY

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ABSTRACT

Ocular albinism is an X-linked recessive inherited syndrome resulting from the variants in the G protein-coupled receptor 143 (*GPR143)* gene. This condition affects patients' vision, characterized by nystagmus, reduced visual acuity, photophobia, retinal hypopigmentation, and foveal hypoplasia, while having minimal effect on skin or hair pigmentation. This study aims to investigate the genetic factor relating to ocular hypopigmentation and nystagmus symptoms in a large family with multiple generations of affected males, which is predicted to be associated with the X-linked inherited model. The first member of this family involved in the genetic examination was a woman with a normal eye phenotype. She had an unaffected daughter, and a son diagnosed with congenital nystagmus and retinal hypopigmentation. Her husband did not have any family history of nystagmus or other ocular abnormalities. Whole-exome sequencing revealed that she harbored a heterozygous variant, c.501_503delGCT (p.Leu168del), in the *GPR143* gene on the X chromosome, which is known to be related to nystagmus and ocular albinism. The Sanger sequencing showed that this variant presented as heterozygous and hemizygous states in her daughter and her son, respectively. This variant is novel because it is absent in our in-house WES database of 600 Vietnamese and other databases. Our study has extended the understanding of molecular genetics associated with X-linked ocular albinism syndrome in Vietnam, contributing to the rapid, effective diagnosis of patients in Vietnam.

Keywords: Ocular albinism, nystagmus, *GPR143* gene, Whole-exome sequencing.

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INTRODUCTION

Human albinism is a congenital condition that has relative deficiencies of pigment in the skin, hair, and eyes. It can be divided into two distinct types, oculocutaneous albinism (OCA) and ocular albinism (OA). While OCA patients suffer from pigment deficiency in their eyes, hair, and skin, OA patients presented hypopigmentation only in their eyes. The typical ocular features of OA include nystagmus, iris transillumination defect, fundus hypopigmentation, abnormal optic nerve, or impaired visual acuity (Thomas et al., 2023). Among these, nystagmus is the most obvious characteristic, with variable frequency and amplitude across patients. Due to the constant movement of the retina, the brain could neither perceive the movement nor see a clear image. The most prevalent form of OA is known as OA type 1 (or Nettleship-Falls type), while other forms are much rarer and associated with other signs and symptoms like hearing loss.

The OA type 1 (OA1) is X-linked recessive inheritance with an incidence of approximately 1 in 60.000 births and appears mainly in males (Rosenberg & Schwartz, 1999). This disorder is a consequence of mutations in the *GPR143* gene, which is located on Xp22.2, spanning 40kb, containing nine exons, and encoding for G protein-coupled receptor 143 (Schiaffino et al., 1995). This receptor has a crucial role in melanosome biogenesis, organization, and transport mechanisms in pigment cells. The disruption of melanosome formation and function directly involves melanin deficiency. Melanin is the pigment responsible for coloration in the eyes, skin, and hair that plays a critical role in the proper development and function of the retina and visual system (Istrate et al., 2020). When the G protein-coupled receptor cannot activate, the number and size of melanosomes can be affected, leading to abnormal eye structure and function (Levin & Stroh, 2011; Xu et al., 2023).

The OA1 patients can be suggested by ophthalmic examination, including ocular movement, color vision, best-corrected visual acuity assessment, iris translucency, and ophthalmoscopy evaluation (Charles et al., 1992). Moreover, genetic testing is especially helpful when the patient has limited phenotype expression, leading to an uncertain diagnosis. As reported in 2002, 48% of the OA1 mutations are intragenic deletions, and 43% of these are point mutations. At that time, researchers used multiplex PCR and dHPLC to identify putative mutations in the OA1 gene (Hegde et al., 2002). In addition, targeted testing (chromosomal microarray and multigene panel to identify recurrent deletions) and comprehensive genomic testing (whole-exome sequencing or whole-genome sequencing) can be combined to detect variants. In contrast to genomic testing, gene-targeted testing necessitates the doctor to speculate as to which gene or genes are most likely involved (Thomas et al., 2023). Based on the genetic findings, the doctor may give disease prognosis to the patients and seek effective therapy for them.

In this study, whole-exome sequencing (WES) and Sanger sequencing were applied as molecular tools for diagnosis. We identified that a *GPR143* variant was the genetic cause of ocular albinism, leading to nystagmus symptoms in multiple male generations of a Vietnamese family.

MATERIALS AND METHODS

Study subjects and clinical examination

A woman (RGNC001M) visited our Center of Biomedical and Pharmaceutical Research (formerly known as the Institute of Genome Research) to seek genetic counselling about an eye condition that has affected her male family members for over four generations. Her son, who is four years old, has congenital nystagmus and iris hypopigmentation. The collection of family history combined with the disorder symptoms observed only in male members suggests a pattern of X-linked inheritance. Additionally, the father was ophthalmologically normal, and there was no history of eye disease in his family. After discussing with the genetic expert, she agreed to be the first member to participate in the genetic investigation. If the

pathogenic variant is found, her daughter (RGNC001F1.1) and her son (RGNC001F1.2) will also participate in genetic testing under the agreement of their parents.

Genomic DNA extraction

Peripheral blood samples (2 mL) of the mother and her children were collected into tubes containing EDTA.K3 anticoagulants and kept at -20 ℃ until use. The genomic DNA of them was extracted from blood samples by Exgene ™ Blood SV mini 250 p Kit (South Korea).

Whole-exome sequencing (WES)

The genomic DNA of the mother was screened and then analyzed for variants by WES according to the typical workflow as described in our previous publications (Ma et al., 2021; Trang et al., 2022).

Sanger sequencing

Sanger sequencing was used to confirm the presence of candidate pathogenic variants in the mother and her children. Primer pair (*GPR143*_E4F: 5'–GGGCTTTCCTCTGTGT ACATT–3' and *GPR143*_E4R: 5'–GGCTCA TGTATTCCCTGCAAG–3') to amplify genomic DNA containing the exon 4 of the *GPR143* gene was designed by PHUSA Biochem (Can Tho, Vietnam). The polymerase chain reaction thermocycle was following as 95 ^{o}C/5 m; (95 ^{o}C/ 30 s; 60 ^{o}C/30 s; 72 ^{o}C/30 s) × 40 cycles; 72 ^{o}C/8 m. The PCR products were sequenced using a forward primer using ABI Prism BigDye Terminator Cycle Sequencing Kit Version 3.1 on the 3500 ABI Genetic Analyzer system (Applied Biosystems, Waltham, Massachusetts, USA). Sequencing data was assessed for analysis using BioEdit software. The reference sequence of the human *GPR143* gene was available with the numbered NM_000273.3 in the NCBI.

***GPR143* protein analysis**

Clustal Omega was used to align multiple sequence alignments and detect conserved amino acid sequences. The amino acid sequence was obtained from UniProt Knowledgebase (UniProtKB) ID: P51810, and the model protein of *GPR143* was built via SWISS-MODEL, with residue interaction visualized using PyMOL Molecular Graphics System version 3.1.

RESULTS AND DISCUSSION

Clinical findings of probands

The female (RGNC001M) in our study represents the fourth generation of a family with a history of multiple male members affected by nystagmus (Fig. 1a). The mother and her daughter (RGNC001F1.1) had no symptoms of the ophthalmic disorder. Her son (RGNC001F1.2) exhibited slight pink eyes due to hypopigmentation with normal skin and hair color (Fig. 1b). Additionally, he also showed nystagmus characterized by abnormal and involuntary eye movements, with the eyes restricted to horizontal oscillations (Fig. 1c).

***GPR143* variant analysis**

Genomic DNA from the mother was subjected to WES, followed by screening for the potentially causative variants in the ocular albinism related genes. The screening identified a heterozygous variant, c.501_503delGCT (p.Leu168del), located in exon 4 of the *GPR143* gene encoding for G protein-coupled receptor 143. According to the OMIM database, the *GPR143* (OA1) variants are associated with ocular albinism with nystagmus. The c.501_503delGCT is a novel variant that has not been reported in the ClinVar, 1000 Genomes Project, and LOVD *GPR143* database (Table 1), and it is considered to delete one amino acid in the transmembrane region of a functional protein.

Sanger sequencing confirmed the presence of the c.501_503delGCT (p.Leu168del) variant in exon 4 of the *GPR143* gene in the mother and two siblings. The genetic variant results in a deletion in the wild-type sequence, leading to the removal of a Leucine residue at position 168 in the *GPR143* protein (Fig. 2a). The mother and the elder daughter are carriers of the heterozygous *GPR143* variant, while the younger son harbors the hemizygous one (Fig. 2b). The observed segregation of genotype and phenotype is consistent with an X-linked dominant inheritance pattern.

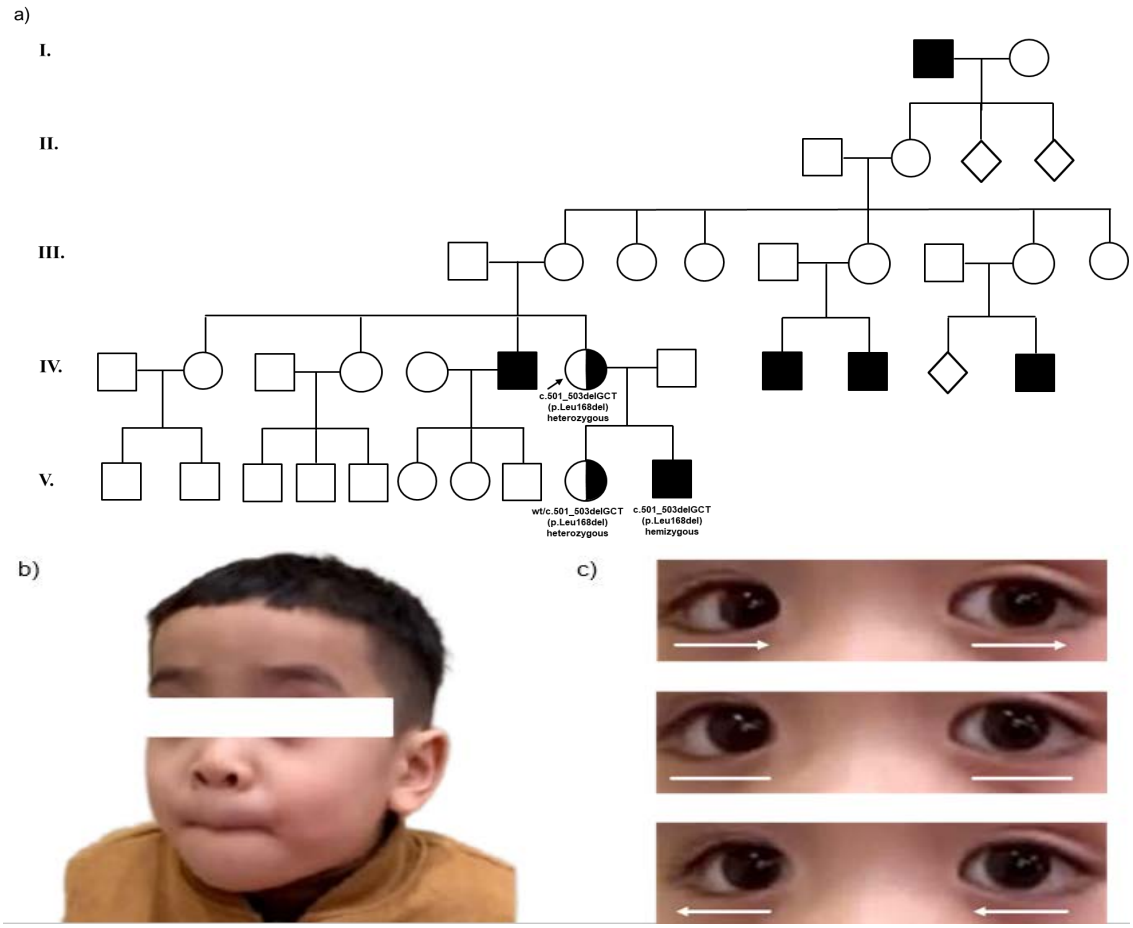

Figure 1. a) Patient's family pedigree in which nystagmus syndrome was found to follow a pattern of X-linked inheritance. Arrows indicate the patient whose DNA genome was applied for WES analysis. Squares, circles, and diamonds represent males, females, and unknown gender, respectively. Filled symbols - affected patients, half-filled - carriers; Phenotype expression of the affected child. b) Patient with normal skin and hair color. c) Uncontrolled ophthalmic movement phenotype of RGNC001F1.2 patient

Table 1. Genetic variant screening by WES

Gene	Variant change		Zygosity	Region	Frequency in 1000G	ClinVar	LOVD
	cDNA	Amino acid					
GPR143 (NM_000273.3)	c.501_503delGCT	p.Leu168del	het	exon 4	-	-	-

GPR143 encodes a 404–amino acid G protein-coupled receptor that functions as a receptor for tyrosine, L-DOPA, and dopamine (Xu et al., 2023). Upon binding L-DOPA, it facilitates calcium ion (Ca^{2+}) influx into the cytoplasm, enhances the secretion of the neurotrophic factor SERPINF1, and promotes the relocalization of beta-arrestin to the plasma membrane. This ligand-dependent signalling operates through a G(q)-mediated pathway in melanocytic cells (Poulain et al., 1991). *GPR143* is widely distributed in melanocytes and the retinal pigment epithelium (RPE), and it is only expressed in melanosomes, which are

a type of intracellular organelle (Palmisano et al., 2008). However, it has not been classified into any class of G protein-coupled receptor (GPCR) family. Neither the exact functions nor the signaling pathways of *GPR143* can be readily determined, especially in the field of disease pathophysiology. However, researchers suggested that the *GPR143* protein can belong to class A (rhodopsin-like receptor) of the GPCR family with functionally diverse receptor members. The rhodopsin-like group mediates diverse physiological processes, including intracellular and intercellular communication, chemotaxis, neurotransmission, and vision (Bueschbell et al., 2022). According to the multiple sequence alignment of the *GPR143* protein result, leucine at position 168 was conserved among Danio rerio, Bos taurus, Mus musculus, Rattus norvegicus, and Homo sapiens (Fig. 2c). The leucine deletion in the conserved region can affect the tertiary or quaternary structure of the *GPR143* protein, altering its function or stability.

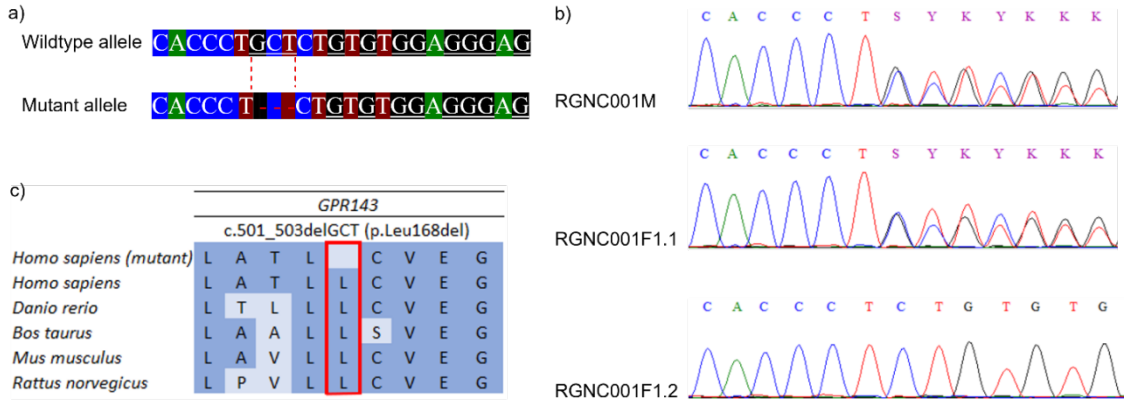

Figure 2. Genetic and evolutionary analysis of the p.Leu168del variant in the *GPR143* gene. a) Sequence comparison between wild-type and mutant alleles. b) Sanger sequencing chromatograms of c.501_503delGCT (p.Leu168del) variant in exon 4 of *GPR143* gene in three samples (RGNC001M - mother, RGNC001F1.1 - daughter, RGNC001F1.2 - son). c) Sequence alignment of the *GPR143* protein (a red frame noted amino acid p.Leu168 position)

The Ocular alb (Ocular albinism type 1 protein; PF02101) domain spans from amino acid 1 to amino acid 395, covering nearly the entire GPR143 protein. Leucine is a hydrophobic amino acid located at position 168 and critical for maintaining the integrity of transmembrane domains (Fig. 3a). Its deletion could destabilize the fourth transmembrane domain (TM4) between the N-terminal and C-terminal domains of the *GPR143* protein, leading to local distortions in the protein structure. This mutation disrupts the original polar contacts, such as those between Leu168 and Gly172, and Leu167 with Glu171 and Gly163. After the deletion, Leu167 forms new polar contacts with Leu164 and Thr166, indicating a significant shift in the interaction landscape (Fig. 3b-ii). The *GPR143* gene encodes a G protein-coupled receptor involved in melanosome biogenesis and function. Therefore, these structural changes may affect the protein's stability and function, with implications for melanosome biogenesis, contributing to hypopigmentation in the retina, abnormal development of visual pathways, and other clinical features of OA1. While the specific p.Leu168del variant in the TM4 domain lacks direct documentation, analogous mutations and deletions in the *GPR143* gene have been associated with protein misfolding, mislocalization, disrupted melanosome function, and clinical conditions such as ocular albinism type 1. Our findings with

abnormal ophthalmic phenotype can be a high probability of causing abnormal *GPR143* gene function in the patients. Although the mother and the eldest daughter are carriers of the *GPR143* gene without exhibiting symptoms, they remain capable of transmitting the mutation to their offspring in subsequent generations. Detecting the mutation is crucial when individuals in later generations plan to have children.

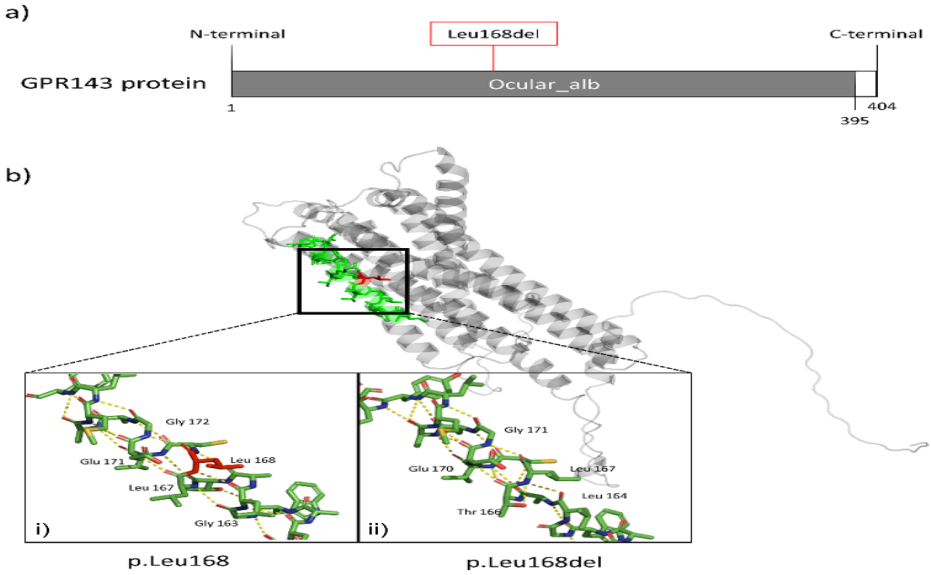

Figure 3. Structural model and functional impact of the wild-type and mutant *GPR143* protein. a) Schematic representation of GPR143 protein domains. b) Structural analysis of i) wild-type at position Leu168 and ii) the p.Leu168del variant (The amino acid Leu168 was highlighted in red, and the box regions indicated the local structural change in the 3D model of *GPR143*)

CONCLUSION

In summary, our study successfully used comprehensive WES to identify a novel variant in the *GPR143* (OA1) gene that caused nystagmus and OA syndrome in a family. Our new findings contribute to the OA genetic database in the Vietnamese population and provide useful information for accurate diagnosis, genetic counselling, and managing cases of OA in Vietnam.

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