A novel variant in *PAX6* as the cause of aniridia in a Chinese family

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Research article

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Abstract

Background: Aniridia is a kind of congenital human panocular anomaly, which is related to *PAX6* commonly.

Methods: The ophthalmic examinations including visual acuity, slit lamp and fundoscopy examination were preformed in a Chinese aniridia pedigree. The targeted next-generation sequencing of Aniridia genes was used to identify the causative mutation.

Results: A novel heterozygous *PAX6* nonsense mutation c.619A>T (p.K207*) was identified in the Chinese autosomal dominant family with aniridia. Phenotypes related to the novel mutation include nystagmus, iris defect, cataract and absence of macular fovea.

Conclusion: The novel nonsense variation in *PAX6* was the cause of aniridia in this family, which expands the spectrum of the *PAX6* mutation and its associated phenotype.

Background

Aniridia is a kind of rare congenital human ocular anomaly; it could manifest either as ocular abnormalities of iris hypoplasia, foveal hypoplasia, cataract, glaucoma, corneal dystrophy, as well as abnormalities of the optic nerve, or as syndromes of the WAGR syndrome (MIM#194072) and the Gillespie syndrome (MIM#206700)[1, 2]. According to pathogenic genes, aniridia can be divided into three types, aniridia-1 (AN1, MIM #106210) aniridia-2 (AN2, MIM #617141) and aniridia-3 (AN3, MIM #617142). AN1 is caused by heterozygous mutation in the *PAX6* gene, AN2 is caused by heterozygous mutation in a *PAX6* cis-regulatory element that resides in an intron of the adjacent *ELP4* gene, and AN3 is caused by heterozygous mutation in the *TRIM44* gene[3–5]. The isolated aniridia was also rarely caused by mutations in *FOXC1* or *PITX2*. Mutations in these genes were more commonly associated with juvenile onset glaucoma and anterior segment dysgenesis presenting with syndromic features of rare cardiac anomalies for *FOXC1* and hypodontia and umbilical anomalies for *PITX2*[6–8].

Aniridia is a rare inherited disease with an incidence estimated between 1 per 50.000 and 96.000 births[9]. More than 80% of the cases were due to monoallelic *PAX6* mutation. About one-third of the cases carry de novo variants[10]. The classical AN1 associated with *PAX6* haploinsufficiency presented iris hypoplasia and foveal hypoplasia, while heterozygous missense mutations in *PAX6* would lead to other ocular diseases including anterior segment dysgenesis and optic nerve malformations.

PAX6 (OMIM 607108), *paired box gene 6*, is a member of the paired box gene family which encodes a transcriptional regulator involved in oculogenesis and other developmental processes[11]. This transcription factor has shown functional conservation in developmental pathways. *PAX6* variant had been identified associated with aniridia and other ocular development abnormalities previously, while olfactory abnormalities and brain structure alterations in line with expression of Pax6 have also been documented recently[12]. *PAX6* played an important role in the process of development regulation which broadly expressed and was controlled by a number of long-range control elements and homozygous mutation led to more severe phenotype[12].

In the present study, we identified novel heterozygous *PAX6* nonsense mutation c.619A > T (p.K207*) in a Chinese autosomal dominant family with aniridia. We used targeted next-generation sequencing (NGS) to screen all the genes related to iris diseases including aniridia and identified the causative mutations.

Methods

The Institutional Review Board (IRB) of Hainan hospital of Chinese PLA General Hospital (Hainan Province, China) approved the present study. All participating family members provided an informed written consent and were endorsed by their respective IRB. The whole procedure of the present study adhered to the tenets of the Declaration of Helsinki.

A small pedigree with aniridia from Hainan province, China, was recruited for the present study. This family included two affected and two unaffected members, which was analyzed and followed up clinically at Hainan Hospital of Chinese PLA General Hospital (Fig. 1A). Comprehensive ophthalmological examinations, including best correct visual acuity (BCVA), applanation tonometry, dilated funduscopy, anterior segment and fundus photography, ultrasound biomicroscopy (UBM) examination, gonioscopy and optical coherence tomography (OCT) of anterior segment and macular were performed on the affected individuals, as well as on the unaffected family members. Genomic DNA was prepared from peripheral blood lymphocytes of the pedigree members and normal controls using a QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany).

Targeted genes enrichment and sequencing

Target enrichment panel of specific hereditary eye based on the next generation sequencing was used to collect the protein-coding region of 371 targeted genes (designed by MyGenostics, Baltimore, MD), which included 37 genes associated iris diseases. (*PAX6*, *ELP4*, *FOXD3*, *PITX3*, *FOXE3*, *PITX2*, *ADAMTS10*, *FBN1*, *LTBP2*, *ADAMTS17*, *MTHFR*, *TYR*, *MITF*, *PAX3*, *SNAI2*, *SOX10*, *RBP4*, *CHD7*, *TMEM67*, *RPGRIP1L*, *CC2D2A*, *YAP1*, *MAF*, *C12orf57*, *FOXC1*, *B3GLCT*, *NF1*, *GPR143*, *OCA2*, *TYRP1*, *CRYGC*, *ADAMTSL4*, *SALL2*, *IGBP1*, *CYP1B1*, *MYOC*, *SALL1*). The genes related to aniridia, WAGR syndrome, Axenfeld-Rieger Syndrom and other diseases involved iris were covered. The process of specific high throughput sequencing was in conformity to some published articles[13, 14].

Bioinformatics analysis

After HiSeq 2000 sequencing, Solexa QA package and the cutadapt program were used to filter out low quality reads and adaptor sequences and high-quality reads from raw reads were retrieved. Then the clean read sequences was aligned to the human reference genome (hg19) using SOA Paligner program. Subsequently, the single nucleotide polymorphism (SNPs) and the insertions or deletions (InDels) were identified using the SOAPsnp program and GATK program separately. The identified SNPs and InDels were annotated using ANNOVAR program (<http://122.228.158.106/exomeassistant>) and viewed using MagicViewer. Finally nonsynonymous variants were evaluated by four algorithms, Ploypphen, SIFT, PANTHER and Pmut, as described previously to determine pathogenicity.

Mutation verification

After high throughput sequencing, the detected variations were validated by Sanger sequencing in the Chinese family. Primer6.0 was used to design the PCR primer sets and the PCR products were sequenced using a Bigdye terminator v3.1 cycle sequencing kit (ABI, Foster City, CA, USA) and analyzed on an ABI 3730XL Genetic Analyzer. The primers used in this study are listed in Table 1.

Table 1
Primers used for potential pathogenic mutations amplification

Mutation	Gene	Exon	Forward primer (5-3 [′])	Reverse primer (5-3 [′])
c.619A>T	PAX6	2	TCAGACATTTAGTCTTTGAATTACTGG	GAGTTTAAGACTACACCAGGCC

Results

Clinical Findings

There were two affected individuals, the proband and his mother, in this two-generation Chinese family (Fig. 1A). The inheritance pattern of the pedigree was in accordance with autosomal dominant inheritance. The proband (II:4) was a 29-year-old male, he felt low vision and photophobia in both eyes since childhood. His BCVA were 0.2 in right eyes and 0.15 in left eyes, with corrections of -4.25 diopters (D) in the right eye and -0.5 D in the left eye. Ophthalmic examination presented horizontal tremor, complete iris absence, lens cortical lamellar mixing (Fig. 2A and B), and absence of macula central fovea (Fig. 3) in both eyes. The iris defect was so severe that the equator of the lens and ciliary process were exposed (Fig. 2B), which could be observed in anterior segment photography and UBM examination (Fig. 2D). Anterior segment OCT and photograph demonstrated the cornea of both eyes were transparent (Fig. 2C), and the structure of anterior chamber angle could be observed under gonioscopy (Fig. 2E), while macula central fovea structure could not be displayed in photograph and OCT of funds as normal structure (Figs. 3 and 4). Intraocular pressure of both eyes was normal. His mother had similar phenotypes, while her cataract became worse with age and she underwent phacoemulsification and intraocular lens implantation at 52 years old. There were no other systemic diseases except eye abnormalities in all the affects.

Identification of causing mutations

After filtering the candidate variants of the proband in the databases, a nonsense mutation *PAX6* c.619A>T in exon 2 changing codon 207 AAG to the stopcodon TAG (p.K207X) was detected. The mutation was absent in either databases mentioned earlier or reported literatures, which leads to Lysine at 207 position in linker region transforming to a premature termination codon, and finally results in *PAX6* underdosage (Fig. 1B). Then the novel mutation was validated by Sanger sequencing and detected among the family members, which demonstrated that the *PAX6* c.619A>T heterozygous mutation was cosegregated with the aniridia phenotype in this family (Fig. 1A). The affected individuals, the proband and his mother, carried the mutation, while the unaffected members did not. These results suggest that this mutation of *PAX6* c.619A>T is a novel causative mutation for autosomal dominant congenital aniridia.

Discussion

Aniridia refers specifically to a panocular disorder, noticeable iris hypoplasia was one of its characteristics, which was usually accompanied by foveal hypoplasia. The visual acuity of patients were impaired severely and they often displayed nystagmus. Some cases could also present other manifestations including cataract, keratopathy, glaucoma and optic nerve malformations[15, 16]. The severity of iris hypoplasia was different, which could range from complete absence of the iris, through enlargement and irregularity of the pupil mimicking a coloboma, to small slit-like defects in the anterior layer seen only on transillumination with a slit-lamp[3]. In this study, we screened the pathogenic gene mutation for this Chinese aniridia family using an iris diseases panel including 37 targeted genes. Then a novel *PAX6* nonsense mutation c.619A > T (p.K207*) was identified in this family and it was separated from disease phenotype. This mutation induced premature termination codons (PTCs) into the *PAX6* open reading frame, and the mRNAs containing PTCs were degraded by the nonsense-mediated decay process, which resulted in a single-dose deficiency. The phenotype of this novel *PAX6* nonsense mutation was line with classical Aniridia related to *PAX6* haploinsufficiency.

A high proportion of cases of aniridia is associated with mutations in *PAX6* frameshift mutations, splicing site mutations or nonsense mutations and these kinds of variations have been considered to produce premature truncation of the protein or nonsense transcripts, leading to haploinsufficiency while few of them were missense mutations. Aniridia phenotype associated with *PAX6* haploinsufficiency almost present various anterior segment and fundus abnormalities including iris hypoplasia, cataract, glaucoma, corneal opacity, microcornea, lens subluxation, foveal hypoplasia, optic nerve malformations and so on, while that variant aniridia phenotype involving dysplasia of skeleton and central nervous system is mostly caused by missense mutations[16, 17]. The most common clinical manifestations associated with aniridia haploinsufficiency were iris anomalies, nystagmus and foveal hypoplasia, followed by cataracts, glaucoma and corneal opacity. In this Chinese family, the inheritance pattern coincided with autosomal dominant inheritance, and the phenotype of proband is similar to his mother's. The proband and his mother felt photophobia from childhood and ocular examination demonstrated nystagmus, aniridia, cataract and foveal hypoplasia. It was reported that

the severity of iris hypoplasia varied in different *PAX6* cases and lens abnormalities include various degrees and types of cataracts and lens ectopic[18]. The patients of this Chinese family associated with *PAX6* nonsense mutation c.619A > T presented complete absence of the iris and spotted opacification of lens cortex, and other eye abnormalities including glaucoma, corneal opacity could not be observed. However, it was interesting that the phenotypes between two nonsense mutation located in close position and same domain were different. It was reported that a 24-year-old patient with *PAX6* c.607C > T, p.Arg203* presented glaucoma and keratopathy besides nystagmus, aniridia and foveal hypoplasia, who has worse visual function[19]. While the patients in this Chinese family with *PAX6* c.619A > T (p.K207*) have milder phenotype in comparison.

The human *PAX6* gene was cloned in 1991 and has been isolated from both vertebrates and invertebrates. It consists of 14 exons and encodes a transcriptional regulator which has a paired-type DNA-binding domain.

There are 2 distinct DNA-binding subdomains, the N-terminal subdomain (NTS) and the C-terminal subdomain (CTS), in the paired domain, which bind respective consensus DNA sequences to recognize target genes. The human *PAX6* gene produces 2 alternatively spliced isoforms that have the distinct structure of the paired domain.[20, 21]. There have been more than 100 mutations reported in the human *PAX6* database since firstly identified as the genetic cause of aniridia in the small eye mouse[22]. While it is remarkable that the alterations in a conserved non-coding element within the 'critical region' and other cis-regulatory elements also can cause aniridia[23]. *PAX6* whole-gene deletions and telomeric cis-regulatory elements deletions were also identified in some Aniridia patients of negative for intragenic *PAX6* mutations. Consequently, it was suggested that *PAX6* whole-gene direct sequencing combined with and molecular methods of detecting copy number alterations (CNV) such as high-resolution comparative hybridization (HR-CGH) arrays, fluorescence in situ hybridization (FISH), and multiplex ligation-dependent probe amplification (MLPA) is important to improve detection rate for Aniridia associated with *PAX6* variations, which could be more suitable for using in the Aniridia cases of iris diseases panel screening negative[24]. It was suggested greater locus heterogeneity might exist in both isolated and syndromic aniridia than was previously appreciated, therefore the improvement of detection method is helpful to improve the detection rate of pathogenic genes for aniridia. In this study, we just have screened protein-coding region of 37 genes associated iris diseases but ignored conserved non-coding element and CNV of *PAX6*, which should be improved in the future.

Conclusion

In brief, a novel nonsense mutation in *PAX6* (c.619A > T p.K207*) was identified in a in a Chinese family with aniridia, which could cause *PAX6* haploinsufficiency. The phenotype associated with this mutation was analyzed including aniridia, cataract and foveal hypoplasia. The present study expands the mutation spectrum of the *PAX6* gene and its phenotype and it may be helpful in the genetic diagnosis of aniridia.

Abbreviations

WAGR: Wilms tumor, aniridia, genitourinary anomalies and mental retardation syndrome; NGS: Next-generation sequencing; IRB: Institutional review board; BCVA: Best correct visual acuity; UBM: Ultrasound biomicroscopy; OCT: optical coherence tomography; *PAX6*: Paired box gene 6; *ELP4*:Elongator acetyltransferase complex subunit 4; *FOXD3*: Forkhead box D3; *PITX3*: Paired-like homeodomain transcription factor 3; *FOXE3*:Forkhead box E3; *PITX2*: Paired-like homeodomain transcription factor 2; *ADAMTS10*: A disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 10; *FBN1*: Fibrillin 1; *LTBP2*:Latent transforming growth factor-beta-binding protein 2; *ADAMTS17*: A disintegrin-like and metalloproteinase with thrombospondin type 1 motif, 17; *MTHFR*: Methylenetetrahydrofolate reductase; *TYR*:Tyrosinase; *MITF*:Microphthalmia-associated transcription factor; *PAX3*: Paired box gene 3; *SNAI2*: Snail family transcriptional repressor 2; *SOX10*: Sry-box 10; *RBP4*:Retinol-binding protein 4; *CHD7*:Chromodomain helicase dna-binding protein 7; *TMEM67*: Transmembrane protein 67; *RPGRIP1L*: Rpgrip1-like; *CC2D2A*: Coiled-coil and c2 domains-containing protein 2a; *YAP1*: Yes-associated protein 1, 65-kd; *MAF*: Maf bzip transcription factor; *C12orf57*: Chromosome 12 open reading frame 57; *FOXC1*: Forkhead box c1; *B3GLCT*: Beta-3-glucosyltransferase; *NF1*: Neurofibromin 1; *GPR143*: G protein-coupled receptor 143;

OCA2: Oca2 melanosomal transmembrane protein; TYRP1: Tyrosinase-related protein 1; CRYGC: Crystallin, gamma-c; ADAMTSL4: Adamts-like 4; SALL2: Sal-like 2; IGBP1: Immunoglobulin-binding protein 1; CYP1B1: Cytochrome p450, subfamily i, polypeptide 1; MYOC: Myocilin; SALL1: Sal-like 1; SNPs: Single nucleotide polymorphism; PCR: Polymerase chain reaction; PTC: Premature termination codon; NTS: N-terminal subdomain; CTS: C-terminal subdomain; CNV: Copy number alterations; HR-CGH: High-resolution comparative hybridization; FISH: Fluorescence in situ hybridization; MLPA: Multiplex ligation-dependent probe amplification;

Declarations

Ethics approval and consent to participate This study followed the tenets of the Declaration of Helsinki and conducted with approval from the Ethics Committee of the Hainan hospital of Chinese PLA General Hospital. A written informed consent was obtained from each participant.

Consent to publish All the patients has written informed consent for the publication of this article and all accompanying images.

Availability of data and materials All data generated and analyzed during this study were included in this manuscript.

Competing interests The authors declare that they have no conflict of interest.

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Authors' Contributions Conceived and designed the work: HB Huang. Acquired the data and Drafted the work: W Liu. Analyzed the data and substantively revised the work: X Jin.

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Figures

Figure 1

Identification of the heterozygous mutation c.619A>T in PAX6 in a Chinese family with aniridia. (A) Pedigree of the family. Squares indicate males and circles, females. Empty symbols and filled symbols represent the normal and affected individuals, respectively. Wt: wild-type and Mt: mutation. (B) Sequence chromatograms showing the PAX6 c.619A>T mutation identified in this study. The arrows indicate the site of the mutation.

Figure 2

Anterior segment features of the proband. (A and B) anterior segment photography of the proband. (C) Corneal OCT of the proband right eye. (D) Ultrasound biomicroscopy examination of proband right eye. (E) Anterior gonioscopy photographs. The arrows indicate the ciliary process and anterior chamber angle. OD stands for right eye, OS, left eye

Figure 3

Fundus examination of the proband. (A and B) Fundus photography of the proband. The arrows indicate the structural absence of macular fovea area area. (C and D) Macular OCT of the proband.

Figure 4

Macular OCT of the normal control. (A and B) Fundus photography of the normal control. The arrows indicate the normal structure of macular fovea area. (C and D) Macular OCT of the normal control.