

Research Article

Identification of Two CRB1 and AHI1 Pathogenetic Variants in an Iranian Family with Two Syndromic and Non-Syndromic Inherited Retinal Disorders

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Abstract

Background: Leber congenital amaurosis (LCA) is one of the most common inherited retinal disorders characterized by rod-cone dystrophy nystagmus, strabismus, with decreased vision after birth, photophobia, cataracts and keratoconus. In the study, we found different genotypes in patients with two different non-syndromic and syndromic patterns in an Iranian family with autosomal recessive retinitis pigmentosa (arRP). **Materials and methods:** The proband's variant were detected by Next Generation Sequencing (NGS) using True Sight One Clinical Exome (TSO) panel of 234 genes related to Inherited retinal dystrophies. The pathogenicity of the variants was determined based on their allele frequency in the Genome aggregation database (gnomAD), In silico prediction tools for new missense and splicing variants, following that it performed cosegregation data in the family. The variants were confirmed by Sanger sequencing using specific primers. **Results:** Molecular study of NGS and following sanger sequencing showed two variants in different CRB1 and AHI1 genes in the patients of family. In the study in proband (VI:2) revealed a homozygous frameshift variant in the exon 6 of the CRB1 gene (NM_201253.2; c.1576C>T; p. (Arg526*)) and in other member of the family a homozygous missense variant in the exon 15 of the AHI1 gene. Patients affected to LCA and a patient affected to Joubert syndrome (JBTS) presented different clinical features. **Conclusions:** In the present study, NGS is considered as the most new and powerful sequencing technique to detect causal variants in different genes. In the family identified two different molecular genetic characteristics of patients with (LCA) and mild JBTS which is involved retinal degeneration which are known to cause severe inherited retinal dystrophies.

Keywords

Leber Congenital Amaurosis (LCA), Autosomal Recessive Retinitis Pigmentosa (arRP), Next Generation Sequencing (NGS), CRB1, AHI1, Joubert Syndrome (JS)

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1. Introduction

Retinitis pigmentosa (RP) is the most common heterogeneous genetic group of hereditary retinal degenerations. The Prevalence of RP is approximatively 1 in 3000 to 4000 or 1.5 million individuals in the worldwide [1-3]. RP is a clinical and genetic heterogeneous disease with several inheritance patterns [4-6].

They are as autosomal dominant (adRP) (30–40%), autosomal recessive (arRP) (50–60%) and X-linked (XLRP) traits (5–15%). In addition, the existence of complex and mitochondrial forms has been previously reported. RP can manifest as syndromic disease in more than 30% or non-syndromic form in 70-80% of cases [7]. Up to now, more than 80 genes (<https://sph.uth.edu/retnet/>) have been involved as syndromic or non-syndromic forms of RP [8].

Leber congenital amaurosis (LCA; OMIM 204000) is one of the most common retinal disorders that is as the most severe form of retinitis pigmentosa (RP) [9, 10]. Clinical symptoms of LCA include nystagmus, strabismus, with decreased vision from the early in life, photophobia, cataracts and keratoconus. In addition, the most cases of LCA may have a good level of intelligence [11, 12]. The prevalence of LCA is estimated to be 1 case per 30.000-80.000 individuals and about 5% of inherited retinal disorders (IRD) [10, 12]. Although, LCA can rarely be inherited in autosomal dominant form for instance owing to mutations in IMPDH1, CRX or OTX2 gene, it is usually transferred in autosomal recessive inheritance pattern. So far, mutations in 25 genes have been described to cause pathogenesis of LCA including AIPL1, CABP4, CCT2, CEP290, CLUAP1, CRB1, CRX, DTHD1, GDF6, GUCY2D, IFT140 IMPDH1, IQCB1, KCNJ13, LCA5, LRAT, NMVAT1, OTX2, PRPH2, RD3, RDH12, RPE65, RPGRIP1 SPATA7, TULP1 [9]. These genes encode proteins responsible for various retinal functions such as intra-photoreceptor ciliary transport, photoreceptor morphogenesis, phototransduction, vitamin A cycling and others. Among of them, three proteins of CRB1, CRX and GDF6 play a key role in photoreceptor morphogenesis [13]. The expression of CRB1 as a human homolog protein is in the brain and the inner segments photoreceptors. Mutations in the Crumbs homolog 1 (CRB1, MIN #604210) gene could cause early-onset retinal dystrophies (EORD) with various clinical manifestations as Leber congenital amaurosis (LCA) (MIN #613835), early-onset RP (MIN #600105) and cone-rod degeneration [11, 14]. In addition, Mutations in CRB1 gene may lead to progression gradually for several decades. Until now, more than 150 different mutations of CRB1 gene have been reported that they are mostly located in the extracellular region [15].

For the first time, AHI1 gene was reported by different studies in related to Joubert syndrome (JBTS; MIM #213300). However, mutations in 34 genes have been reported to be associated JBTS, AHI1 is one of the most common pathogenic gene accounting for 38% JBTS population. Indeed, mutations in two AHI1 and CEP290 genes have been related to retinal degeneration [16]. The Joubertin protein encoded by

AHI1 gene acts as a scaffold and lead to promote the formation and function of primary cilia [17]. It characterized by dysplasia of cerebellar vermis part, neurological dysfunction, retinal dystrophy, developmental delay and breathing abnormalities [18-20]. Furthermore, the recent findings revealed that AHI1 gene as mild JBTS phenotypes are involved in non-syndromic retinal disorders with mild neurological symptoms or without neurological symptoms [19].

In this study, the disease-causing mutations in two different genes of an Iranian family with 6 affected members were identified by Next Generation Sequencing (NGS) using a panel of 4.900 genes related with known clinical diseases. Thereby, these finding cause to provide essential information for further genetic counseling and gene therapy.

2. Material and Methods

This study was approved by the Ethics Committee of Shahid Saduoghi University of Yazd Medical Sciences (IR.SSU.MEDICINE.REC.1395.91). The consent form, full medical and family history were taken from this large Iranian family. This study carried out based on Declaration Helsinki.

Extraction of the genomic DNA was obtained from all members peripheral blood in the family by using automated DNA extractor BIORobot EZ1 (Qiagen, Hilden, Germany). Measurement of the DNA purity was performed by UV spectrophotometer.

Molecular study was performed in the proband of the family by Next Generation Sequencing (NGS) using True Sight One Clinical Exome (TSO) panel (Illumina, San Diego, CA, USA) in Genetics Department of Fundacion Jimenez Diaz University Hospital Madrid, Spain. TSO library was provided using the manufacturer's instructions and sequenced on the Nextseq500 platform (Illumina). The pathogenicity of the variants was determined based on their allele frequency in the Genome aggregation database (gnomAD), In silico prediction tools for new missense and splicing variants including M-CAP [21], CADD [22] and those included in the commercial Alamut software v2.9.0 (Interactive Biosoftware, Rouen, France), following that it performed cosegregation data in the family. Variants of CRB1 and AHI1 were confirmed by Sanger sequencing using specific primers (F-CRB1-Primer: GCGATGGCTTCCTGTGGG and R-CRB1-Primer: GGTCGCTACCTCTCACCGT) and the variant of AHI1 was confirmed by Sanger sequencing using specific primers (F-AHI1-Primer: CTTGGTTTACCATTGGTCGTT and R-AHI1-Primer: GCGCAATCAGTACATAACC).

3. Case Presentations

The pedigree chart of the family diagnosed with retinitis pigmentosa and an autosomal recessive genetic pattern is

drawn (Figure 1). The proband (VI:2) was a 12-year-old male who presented the clinical phenotype relate to RP disease including nystagmus, night blindness, photophobia in infancy. His older affected brother (VI:1) was 19-year-old and also presented similar age of onset of symptoms and phenotypic features. Ophthalmology examination showed the affected patients had night blindness and impairment of visual acuity (VA) in the early life and gradually developed decline in vision. The fundus photography of the proband's left eye revealed the pigmentary retinal dystrophy with changes of bone spicule in retina area and tortuous veins. Optical coherence topography (OCT) revealed loss of lamination and irregular layer. In the proband's fluorescein angiography showed increasing of macula avascular zone with changes of hypofluorescent and hyperfluorescent spots due to RPE cells injury. Their unaffected parents have consanguineous marriage. Proband's mother (V:2), his maternal affected aunt (V:1) and his two maternal healthy uncles were born from his consanguineous healthy maternal grandfather (IV:5) and grandmother (IV:1). Proband's maternal affected aunt (V:1) was a 35-year-old who clinical symptoms included early visual impairment, severer nystagmus in two eyes, refraction defects and photophobia. Proband, his affected brother and his affected aunt were diagnosed with RP after birth. Her clinical signs were progressed at 16 years old. Cataract surgery was performed on her right eye at 30 years old. Her right eye A-vector & B-mode sonography revealed that there is mild

lobulation of the globe wall. The posterior two-thirds of the globe wall is hyperechoic and shows posterior acoustic shadowing could be due to dense calcification or ossification. The thickness of the crystalline lens is within normal range. The cortex of the lens is echogenic suggestive of mature cataract, most likely to be calcified and slightly subluxated posteriorly. Coronal membrane is seen in anterior third of the posterior segment could be cyclitic membrane or portion of RD.

Proband's maternal cousin (V:5) was a 36 years old affected female who had unaffected parents. She was only patient with clinical phenotype relate to syndromic disease in this family. She presented nystagmus, developmental delay with hypotonia, mild neurological symptoms, poor language skills, walking imbalance mildly, night blindness, loss of peripheral vision at childhood and no respiratory difficulties. Ophthalmology examination exhibited retina pigmentation, thinning of retinal vessels. Other affected patients in the family were diagnosed with RP non-syndromic disease. In addition, there were affected brother (VI:4) a 23-year-old male and sister (VI:3) a 29-year-old female at this family who have distant relatives with the proband. Their unaffected parents had consanguineous marriage. Clinical symptoms of them were similar to proband's signs. but, the affected brother (VI:4) presented keratoconus and the affected sister (VI:3) had nystagmus and also strabismus at 28 years old that it removed without wearing the glasses.

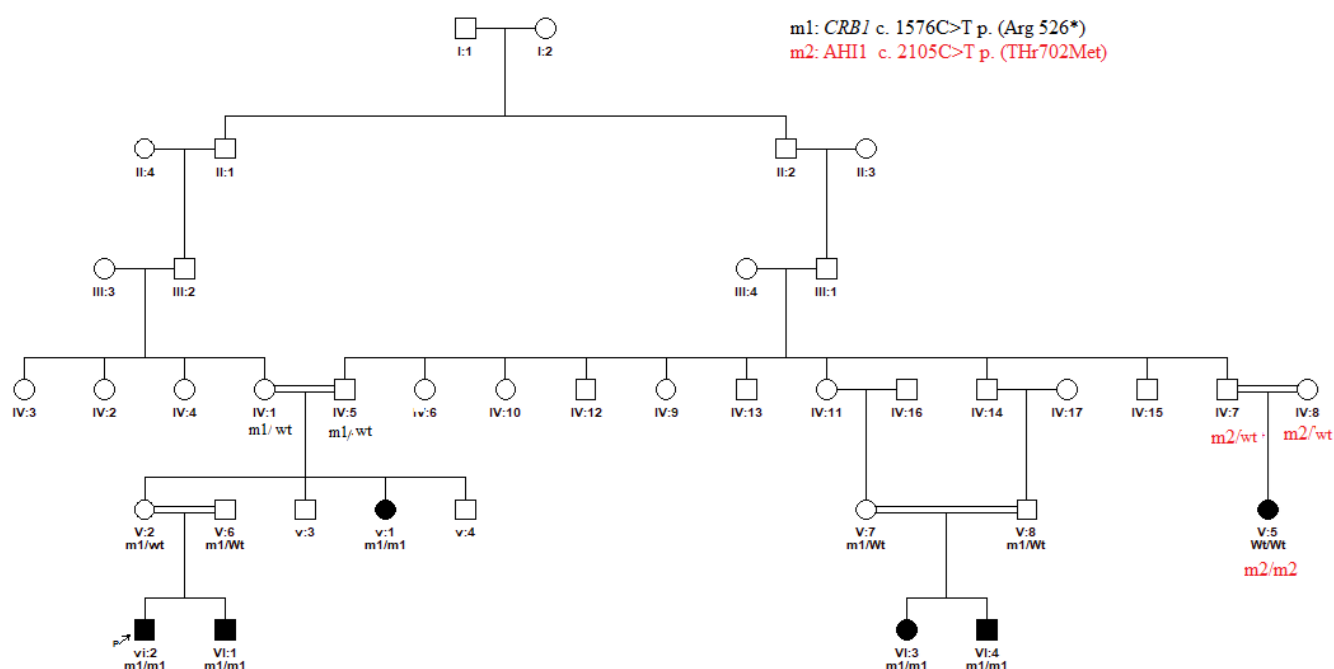


Figure 1. Pedigree of Family with Leber Congenital Amaurosis (LCA) & Joubert Syndrome and Segregation Results of Two Variants *c.1576C>T* (p. Arg 526*) in *CRB1* Gene and *c.2105C>T* (p. Thr702Met) in *AHI1* Gene.

The molecular study by NGS in proband (VI:2) revealed a homozygous frameshift variant in the exon 6 of the *CRB1* gene (NM_201253.2; *c.1576C>T*; p. (Arg526*)) and in other

member of the family a homozygous missense variant in the exon 15 of the *AHI1* gene (NM_017651.4; *c.2105C>T*; p. (Thr702Met)).

Segregation analysis of the variant c.1576C>T in the CRB1 gene performed in the family has confirmed that proband's healthy parents and all patients' unaffected parents in the family are heterozygous. Besides, proband's affected maternal aunt (V:1), two affected individuals of distant relatives (VI:3 & VI:4) are homozygous mutation. Whereas, proband's

maternal cousin (V:5) had a normal CRB1 sequence without any mutation and has confirmed the homozygous mutation in AHI1 gene. The variant was described first time by Suzuki et al. The in-silico prediction tools used classified the variants in CRB1 and AHI1 genes as pathogenic and probably pathogenic, respectively (Table 1).

Table 1. The Variants Found in the CRB1 and AHI1 Genes with in Silico Prediction.

Gene Variant Polyphen Mutation Taster CADD M-CAP SIFT

CRB1 c.1576C>T; p. (Arg526*) N/A Disease causing (1.0) Mildly deleterious (35) N/A N/A

AHI1 c. 2105C>T; p. (Thr702 Met) Probably damaging Disease causing (1.0) Mildly deleterious (32) Possible pathogenic Damaging (0.899) (0.047) (0.009)

4. Discussion

In present study, we report two variants in genes CRB1 (c.1576C>T; (p. Arg 526*)) and AHI1 (c.2105C>T; (p. Thr702Met)) disease-causing two Leber congenital amaurosis (LCA) and Joubert syndrome (JBTS), in an Iranian family with consanguineous marriage. A meta-analysis study of mutations of CRB1 described these mutations as a common disease-causing of childhood-onset retinal disorders which account for over 10.1% of LCA/EORD affected individuals and 2.7% in RP patients [11]. Indeed, over than 194 mutations in CRB1 associated with the pathogenesis of RP with autosomal recessive inheritance pattern in diverse populations that 189 of them are located in extracellular domain [23-25]. The variant (c.1576C>T; (p. Arg 526*)) in CRB1 gene was previously reported [9]. This change has been described in the general population with a low allele frequency (rs114342808; 0.000032; dbSNP & Exome Aggregation Consortium -ExAc-). Mutations in the CRB1 gene have been associated with autosomal recessive forms of cone-rod dystrophies, Leber congenital amaurosis and retinitis pigmentosa, mainly (Human Gene Mutation Database-HGMD) [11]. However, early-onset RP is as a milder form than LCA, their diagnosis in some patients due to high clinical overlap is difficult [14].

The Genotype/phenotype correlation due to the existence of diverse CRB1 associated to retinal phenotypes and different types of mutations such as missense, null mutations (i.e.; frameshift and nonsense) and splice-site in the several studies is unknown [24]. In several previous studies revealed that severe retinal phenotypes instance in LCA might be related to null mutations. Moreover, it would be suggested that the existence of the modifying factors on CRB1 mutations might affect the patients' retinal phenotypes [26].

The incidence of JBTS is estimated between 1:80,000 and 1:100,000 [27-29]. There are six subgroups of JBTS based on the organ involvement [30]. Mutations in AHI1 are the most

common disease-causing type of JBTS with ocular disorders [29]. In the study, the patient (V:5)'s clinical features include defect in primary cilia function, night blindness vision, nystagmus, poor visual acuity, walking imbalance, developmental delay and mild neurological symptoms. Moreover, the mean of age death at patients affected to JBTS is 7.2 years [30], while the age of present case is 36 years old. The findings confirmed as mild JBTS with retinal degeneration. The result has previously been reported in the Chinese patient carrying variant at c.2105C>T (p. Thr702Met) in AHI1 gene [30]. In the present patient, we identified the missense variant at c. 2105C>T (p. T702M) in AHI1 gene which is considered a probably pathogenic variant. T702M variant is located in WD40 domain of Joubertin. The AHI1 gene encodes Joubertin protein which includes a coiled-coil domain in N-terminal, WD40 domain and C-terminal SH3 binding domain [30]. Valente et al, 2006 has been described rare missense mutations in exons and introns of AHI1 gene might modify Joubertin protein truncation and lead to loss of function and most null mutations (nonsense and frameshift mutations) lead to alter structure in the protein [26]. Although, Nguyen et al, 2017 reported missense mutations in the WD40 domain could lead to non-syndromic RP with mild manifestations and late-onset [31]. Suzuki et al, 2016 reported the variant p. 702M in AHI1 gene in a compound heterozygous pattern with the AHI1 gene c.903_910insA p.304fs*309 insertion. The clinical symptoms reported as JBTS without ocular defects [32], whereas, other study has showed a pathogenic pattern of AHI1 gene p. E281* with clinical manifestations including retinal degeneration and pure JBTS in the patients.

The findings revealed that there are any correlations between clinical features of patients and the type variant of AHI1 gene. Besides, the effect of T720M on Joubertin protein conformation and its function is ambiguous [30].

In conclusion, we found two different variants in two CRB1 and AHI1 genes causing LCA disease and mild JBTS with retinal defects with diversity clinical manifestations in an

Iranian family. CRB1 mutations is one of the most common causes of LCA and early-onset RP in the Iranian populations.

Abbreviations

LCA	Leber Congenital Amaurosis
ArRP	Autosomal Recessive retinitis Pigmentosa
NGS	Next Generation Sequencing
CRB1	Crumbs Cell Polarity Complex Component
AHI1	Abelson Helper Integration Site 1
JBTS	Joubert Syndrome

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Conflicts of Interest

The authors declare no conflicts of interest.

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