Whole Exome Sequencing in Eight Thai Patients With Leber Congenital Amaurosis Reveals Mutations in the CTNNA1 and CYP4V2 Genes

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Purpose. Our goal was to describe the clinical and molecular genetic findings in Thai patients with Leber congenital amaurosis (LCA).

Methods. Whole exome sequencing (WES) was performed in eight unrelated patients. All genes responsible for inherited retinal diseases (IRDs) based on RetNet were selected for analysis. Potentially causative variants were filtered through a bioinformatics pipeline and validated using Sanger sequencing. Segregation analysis of the causative genes was performed in family members when available.

Results. Eleven deleterious variants, six nonsense and five missense, were identified in seven genes: four LCA-associated genes (CEP290, IQCB1, NMNAT1, and RPGRIP1), one gene responsible for syndromic LCA (ALMS1), and two IRDs-related genes (CTNNA1 and CYP4V2). Clinical reassessment supported the diagnosis of syndromic LCA in those patients harboring potentially pathogenic variants in the ALMS1. Interestingly, two causative genes, CTNNA1 and CYP4V2, previously reported to cause butterfly-shaped pigment dystrophy (BSPD) and Bietti's crystalline dystrophy (BCD), respectively, were detected in two other patients. These two patients developed rapid and severe visual loss in contrast to BSPD and BCD patients in previous studies. The results of this study demonstrate that causative variants identified in the CTNNA1 and CYP4V2 genes are also associated with LCA.

Conclusions. This is the first report describing the molecular genetics and clinical manifestations of Thai patients with LCA. The present study expands the spectrum of LCA-associated genes, which is a benefit for molecular diagnosis. The identification of mutations in the CTNNA1 and CYP4V2 genes requires further elucidation in larger cohorts with LCA.

Keywords: whole exome sequencing, Leber congenital amaurosis, molecular genetics, Thai, inherited retinal diseases

Leber congenital amaurosis (LCA; Mendelian Inheritance in Man [MIM #204000]) is the most severe form of inherited retinal diseases (IRDs), with onset in the first few months after birth or in early childhood. It has an estimated worldwide prevalence between 1:30,000 and 1:80,000.1 The clinical hallmarks of LCA include wandering nystagmus, ocudigital sign, high hyperopia, photophobia, sluggish or near-absent pupillary responses, and severely reduced rod and cone responses on the electroretinogram (ERG). Leber congenital amaurosis is a clinically heterogeneous disease. Not only the ocular features were observed, but systemic manifestations, such as diabetes mellitus, renal failure, sensorineural hearing loss, and neurodevelopmental delay and intellectual disability, have also been reported in the patients who were initially diagnosed with LCA. Some syndromic diseases, including Alström syndrome, Bardet-Biedl syndrome, Batten disease, Joubert syndrome, and Senior-Loken syndrome, exhibit additional clinical presentations that overlap with LCA.1 Leber congenital amaurosis is also a genetically heterogeneous disease, showing both autosomal recessive (ar) and autosomal dominant (ad) inheritance patterns. Mutations in at least 24 genes have been implicated in nonsyndromic LCA (RetNet; in the public domain, https://sph.uth.edu/retnet/sum-dis.htm): 22 genes for arLCA (AIPL1, CABP4, CEP290, CLUAP1, CRB1, CRX, DTHD1, GDF6, GUCY2D, IFT140, IQCB1, KCNJ13, LCA5, LRAT, NMNAT1, PRPH2, RD3, RDH12, RPE65, RPGRIP1, SPATA7, and TULP1) and three genes for adLCA (CRX, IMPDH1, and OTX2). The gene CRX displays both patterns of inheritance. Disease-causing genes have been identified in approximately 70% of LCA cases.1
Due to the clinical and genetic heterogeneity of LCA, molecular diagnostic testing is necessary to provide information for diagnostic accuracy. Recently, whole exome sequencing (WES), an efficient and cost-effective molecular diagnosis tool, has been used to identify disease-causing genes in LCA.\(^2\)\(^-\)\(^7\)

This is the first report of WES being conducted in Thai patients with LCA. We performed WES in eight unrelated Thai patients clinically diagnosed with LCA. Eleven potentially causative variants, five novel and six known, in seven genes were identified. Remarkably, two genes, CTNN4A1 and CYP4V2, previously reported in other adult-onset inherited retinal degenerations, have been demonstrated to be associated with severe congenital visual impairment.

**Materials and Methods**

**Subjects and Clinical Assessment**

The study protocol was approved by the ethics committees of the institutional review board of Siriraj Hospital Mahidol University and adhered to the tenets of the Declaration of Helsinki. Eight unrelated patients with a clinical diagnosis of LCA were recruited from the Division of Ophthalmology, Siriraj Hospital, Bangkok, Thailand. All participants underwent detailed ophthalmologic examinations, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated-pupil fundus examination, cycloplegic refraction, full-field ERG, flash visual evoked potential (FVEP), and optical coherence tomography (OCT) when available. After informed consent was obtained from the patients or their parents, venous whole blood samples were collected for molecular genetic testing.

**Whole Exome Sequencing (WES) and Bioinformatics Analysis**

Genomic DNA preparation, exome capture, Illumina sequencing, and variant-calling pipelines were performed as described previously.\(^8\) Annotation of variants obtained from each patient was performed according to the wANNOVAR web server (in the public domain, http://wannovar.wglab.org/index.php).\(^9\)

**Variant Identification**

Initially, variants identified in 24 candidate genes for LCA were selected for data analysis and variant filtering. For patients with no mutations, 235 IRD-associated genes reported in the RetNet database were further analyzed. By following the American College of Medical Genetics and Genomics (ACMG) guidelines,\(^10\) the nucleotide sequence variants identified in this study were classified into five classes: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Variants were classified as causative based on patterns of inheritance of each gene with the following criteria: (1) missense or nonsense variant, (2) reported as deleterious by at least two out of three prediction tools: PolyPhen2 (in the public domain, http://genetics.bwh.harvard.edu/pph2/), SIFT (in the public domain, http://sift.jcvi.org/), and MutationTaster (in the public domain, http://www.mutationtaster.org/), (3) located at the donor or acceptor splice site, (4) not observed in the dbSNP database built 138 (in the public domain, ftp://ftp.ncbi.nlm.nih.gov/projects/SNP/), 1000 Genomes Project (in the public domain, ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp), Exome Variant Server (EVS; in the public domain, http://evs.gs.washington.edu/EVS/), or Exome Aggregation Consortium (ExAC; in the public domain, http://exac.broadinstitute.org/). However, the disease-associated variants in genes that are inherited as ar traits may also be present in the heterozygous state in publicly available databases. Mutations specified in the Human Gene Mutation Database (HGMD; in the public domain, http://www.hgmd.cf.ac.uk/ac/index.php) or those characterized as deleterious variants in previous studies were considered as disease causing. HOPE (in the public domain, http://www.cmbi.ru.nl/hope/) was used for the prediction of protein structures and functions of missense variants.\(^11\) The Variant Call Format (VCF) output files that detail the deleterious variants were loaded into the Integrative Genomics Viewer (IGV; in the public domain, http://www.broadinstitute.org/igv/) to visualize the exome coverage and base calls. Multiple sequence alignments of the amino acid residues across species were generated using the ClustalW online tool (in the public domain, http://workbench.sdsc.edu/).

**Sanger Sequencing and Segregation Analysis**

Sanger sequencing confirmed predicted deleterious variants in the candidate genes. Specific primers were designed with the Primer3 program (in the public domain, http://bioinfo.ut.ee/primer3/) using NCBI37/hg19 as the reference sequence. Sanger sequencing also performed segregation analysis of pathogenic or likely pathogenic variants in available family members. Novel nucleotide substitution variants that were likely to be deleterious and also segregated within the families were subsequently screened in 130 ethnically matched control subjects by denaturing high-performance liquid chromatography (Transgenomics, Omaha, NE, USA).

**Results**

WES was performed to identify the disease-causing genes in eight unrelated Thai patients with LCA. According to our criteria for variant analysis, we identified 11 different single-base substitutions (6 nonsense and 5 missense) in seven genes associated with LCA, syndromic LCA, and other IRDs. A summary of the clinical information, fundus images, family pedigrees, and the pathogenic variants identified in this study are shown in Table 1, Figure 1, Figure 2, and Table 2, respectively. However, the fundus photograph for patient LCATH4 was not available. The fundus description in Table 1 is only based on a fundoscopic examination. All nucleotide alterations, except for the variant detected in patient LCATH5 and LCATH7, segregated in trans in the available family members without disease manifestations.

**Pathogenic Variants Identified in LCA-Associated Genes**

Pathogenic variants in four candidate genes for LCA (CEP290, IQCB1, NMNAT1, and RPGRIP1) were identified in four of eight patients (Table 2). Patient LCATH1, a 6-month-old male, harbored novel compound heterozygous nonsense variants, p.Gln123Ter and p.Glu543Ter, in the CEP290 gene. Patient LCATH2 is a 4-year-old female, who carried a novel homozygous variant, p.Lys315Ter, in the IQCB1 gene. Patient LCATH3, a 13-month-old male, carried previously reported compound heterozygous missense mutations, p.Arg667Trp and p.Val212Met, in the NMNAT1 gene. Patient LCATH4, a 6-month-old male, harbored a previously reported homozygous variant for p.Arg371Ter in the RPGRIP1 gene.

**Pathogenic Variants Detected in Syndromic LCA-Associated Gene**

Deleterious truncating variants in gene associated with syndromic LCA were observed in two patients (Table 2). Two
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age of Onset</th>
<th>Presenting Symptoms</th>
<th>Age at Initial Examination</th>
<th>BCVA</th>
<th>Lens</th>
<th>Fundus</th>
<th>ERG</th>
<th>FVEP</th>
<th>Refraction</th>
<th>Extraretinal Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCATH1</td>
<td>Male</td>
<td>4 mo</td>
<td>History of not fixing on and following objects</td>
<td>6 mo</td>
<td>Wandering eye</td>
<td>Wandering eye</td>
<td>Clear</td>
<td>Clear</td>
<td>Pink disc, artery attenuation, mild RPE changes midperiphery, no bone spicules</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>LCATH2</td>
<td>Female</td>
<td>1 y</td>
<td>Nystagmus</td>
<td>4 y</td>
<td>6/24</td>
<td>5/60</td>
<td>Clear</td>
<td>Clear</td>
<td>Pink disc, artery attenuation, generalized RPE changes, no bone spicules, maculopathy with RPE atrophy and pigment clumps</td>
<td>NR</td>
<td>Normal</td>
</tr>
<tr>
<td>LCATH3</td>
<td>Male</td>
<td>1 y</td>
<td>History of holding things too closely to his face, mild nystagmus</td>
<td>13 mo</td>
<td>Wandering eye</td>
<td>Wandering eye</td>
<td>Clear</td>
<td>Clear</td>
<td>Pale disc, artery attenuation, generalized RPE changes with bone spicules, maculopathy with RPE atrophy and pigment clumps</td>
<td>NR</td>
<td>Mildly delayed latency and decreased amplitude, BE</td>
</tr>
<tr>
<td>LCATH4</td>
<td>Male</td>
<td>Birth</td>
<td>History of not fixing on and following objects</td>
<td>7 mo</td>
<td>Not fixing on and following</td>
<td>Not fixing on and following</td>
<td>Clear</td>
<td>Clear</td>
<td>Mild pale disc, generalized RPE changes, no bone spicules</td>
<td>NR</td>
<td>Normal</td>
</tr>
<tr>
<td>LCATH5</td>
<td>Male</td>
<td>Birth</td>
<td>History of blurred vision since birth</td>
<td>6 y</td>
<td>6/120</td>
<td>6/240</td>
<td>Clear</td>
<td>Early PSC</td>
<td>Pale disc, artery attenuation, generalized RPE changes, no bone spicules</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>LCATH7</td>
<td>Male</td>
<td>Birth</td>
<td>History of not fixing on and following objects</td>
<td>5 mo</td>
<td>Not fixing on and following</td>
<td>Not fixing on and following</td>
<td>Clear</td>
<td>Clear</td>
<td>Pale disc, artery attenuation, generalized RPE changes with bone spicules, maculopathy with RPE atrophy and pigment clumps</td>
<td>NR</td>
<td>Normal</td>
</tr>
</tbody>
</table>
patients, LCATH5 and LCATH6, demonstrated pathogenic variants in the ALMS1 gene, a causative gene for Alström syndrome (AS). Molecular findings in patient LCATH5, a 6-year-old male, showed compound heterozygous nonsense variants; a reported mutation, p.Ser1299Ter, and a novel variant, p.Glu2681Ter. Due to the lack of DNA samples from additional family members, we were unable to confirm the segregation of these two variants in this family. Patient LCATH6, a 6-year-old male born to consanguineous parents, carried a reported homozygous nonsense mutation of p.Ser1299Ter in the ALMS1 gene. Cosegregation analysis confirmed that p.Ser1299Ter variants were inherited from heterozygous carrier parents (Fig. 2).

Pathogenic Variants Identified in Other IRDs Genes

In our study, we identified two patients carrying three deleterious variants in two genes (CTNNA1 and CYP4V2) associated with other types of retinal degenerations. Patient LCATH7, a 5-month-old male, harbored a novel heterozygous missense variant, p.Gly353Cys, in the CTNNA1 gene, which causes butterfly-shaped pigment dystrophy (BSPD) (Table 2). The p.Gly353Cys variant is predicted to be deleterious by multiple in silico algorithms and was not observed in all public variant databases and a cohort of 130 control subjects. Cosegregation analysis was performed only in the mother. The result showed that the unaffected mother carried normal alleles. Additionally, a novel single heterozygous missense variant, c.C5414T (p.Pro1805Leu), which was predicted to be deleterious was also identified in the KIAA1549 gene associated with ar retinitis pigmentosa (RP).

Genetic analysis in patient LCATH8, a 2-year-old male from a consanguineous family, revealed the compound heterozygous missense variants, p.Glu79Asp and p.Met123Val, in the CYP4V2 gene (Table 2). Both variants were previously reported in a patient with Bietti crystalline corneoretinal dystrophy (BCD). Furthermore, a novel single heterozygous nonsense variant, c.C10819T (p.Arg3607Ter), in the ALMS1 gene associated with arAS has also been found.

Clinical Reassessment of Patients Harboring Pathogenic Variants in Syndromic LCA-Associated Gene and Other IRDs Genes

To elucidate the association between the clinical and genetic findings for the ambiguous cases, clinical re-evaluation was performed in patients LCATH5 and LCATH6 who carried pathogenic variants in syndromic LCA-associated gene (ALMS1), and patients LCATH7 and LCATH8 who carried pathogenic variants in other IRDs genes (CTNNA1 and CYP4V2). The results showed that patients LCATH5 and LCATH6 had systemic manifestations consistent with the clinical phenotype of AS (Table 1). Both patients demonstrated the key features of AS including childhood obesity, sensorineural hearing loss, and retinal dystrophy. Patient LCATH5 developed myocarditis, asthma, and pneumonia while patient LCATH6 had hypertriglyceridemia and normal echocardiogram.

Mutations in the CTNNA1 gene have been reported in BSPD, with onset in young to middle-aged adults and a BCVA between 20/20 and 20/200. Patient LCATH7, with the CTNNA1 variant, was unable to fix and follow an object at the age of 5 months (Table 1). Fundus photographs demonstrated atrophic macula with circinate pigmentation in both eyes similar to the wings of a butterfly (Fig. 1). Follow-up examination at 8-years old showed wandering eye movement with sunken eyes.
Mutations in the CYP4V2 gene have been reported in BCD, with onset in young- to middle-aged adults. The presence of multiple glistening intraretinal crystals scattered throughout the fundus is the hallmark of this condition. Patient LCATH8, who carried two previously reported mutations in the CYP4V2 gene, had a history of nystagmus and photophobia since age 1 year (Table 1). His visual acuity worsened rapidly from counting fingers at 5-years old to hand motion at the age of 7. Fundus examination disclosed generalized hypopigmented mottling of the RPE and patchy hyperpigmentation in the macular area (Fig. 1). We did not observe the typical crystals or lipid deposits normally shown in BCD.

**DISCUSSION**

Using WES, we identified pathogenic variants in all eight patients initially diagnosed with LCA. Among these patients, four harbored causative variants in the reported genes associated with LCA (CEP290, IQCB1, NMNAT1, and RPGRIP1), two carried causative variants in the gene responsible for syndromic LCA (ALMS1), and two were found to carry IRDs-associated genes (CTNNA1 and CYP4V2).

Variable clinical expression in patients with the CEP290 mutations have been reported, ranging from nonsyndromic LCA to severe systemic conditions, such as Joubert syndrome, characterized by retinal dystrophy and progressive cystic kidney disease; Bardet-Biedl syndrome, characterized by retinal degeneration, obesity, polydactyly-type limb anomalies, renal failure, cognitive impairment, hypothagamidism, and genital anomalies; and Meckel syndrome, a lethal disease, characterized by central nervous system defect, bilateral renal cystic dysplasia, polydactyly, and hepatic developmental defects. In this study, patient LCATH1 carried a novel compound heterozygous nonsense variants in the CEP290 gene. The patient had a history of not fixing on and following objects since 4 months of age. Follow-up examination at the age of 6 years showed the same clinical symptoms (Table 1) without systemic manifestations. Because systemic abnormalities are not apparent until late childhood or adulthood, further renal function tests of patient LCATH1 should be done for surveillance and treatment planning.

Mutations in the IQCB1 gene have been identified in both patients with Senior-Loken syndrome (SLS) and LCA. In our study, patient LCATH2 harbored a novel homozygous nonsense variant in the IQCB1 gene. The patient had a history of nystagmus developing in the first year of life. A follow-up investigation at the age of four years showed two simple cysts in the right kidney (Table 1). Regular follow-up examinations should be performed to determine the progressive renal function decline.

From previous reports, most of the patients with NMNAT1-associated LCA had the same phenotype, including severe visual impairment and central macular atrophy from birth. In this study, patient LCATH3, who carried the reported compound heterozygous missense variants in the NMNAT1 gene, showed consistent findings with generalized RPE changes, attenuated arterioles, pigment alteration, and demarcated circular atrophic area in the macula region, demonstrat-
ed at the age of 13 months (Fig. 1). Our results support the genotype–phenotype characterization in patients with NMNAT1-associated LCA.

Mutations in the RPGRIP1 gene can cause both LCA and cone–rod dystrophy.20 In this study, patient LCATH4 harbored a known homozygous nonsense variant, p.Arg371Ter, in the RPGRIP1 gene. This patient had a history of not fixing on and following objects with oculodigital sign and developmental delay at age 7 months. Computed tomography scan shows focal atrophy of the frontal lobe. Neurodevelopmental delay has also been reported in three LCA patients with RPGRIP1 mutations.21,22 Although p.Arg371Ter was a reported disease-causing variant in an LCA patient,14 no clinical data have been described. Therefore, we cannot compare phenotypic features between these two patients. From all of these data, our results are in accordance with previous findings21 that disease-causing variants in the RPGRIP1 gene can be observed in LCA patients with or without neurodevelopmental abnormalities.

The ALMS1 gene was characterized as a causative gene for A5, a rare autosomal recessive syndromic form of LCA, with an estimated prevalence of less than 1 in 1,000,000.23 In this study, two unrelated patients, LCATH5 and LCATH6, carried pathogenic variants in the ALMS1 gene and had phenotypes consistent with A5. The null alleles, p.Ser1299Ter and p.Glu2681Ter, are localized in exons 8 and 10, respectively (Table 2). These findings, in accordance with previous studies, showed that most ALMS1 mutations are either nonsense or frameshift mutations and are located in exon 16, exon 10, and exon 8.23 Although both patients, LCATH5 and LCATH6, harbored the same pathogenic mutation (p.Ser1299Ter), the allelic state detected from each patient was different (i.e., heterozygous in LCATH5 and homozygous in LCATH6). The results from clinical re-evaluation imply that patient LCATH5 had a more severe phenotype with heart disease and chronic respiratory tract infection.

The CTNNAI gene encodes catenin alpha 1, which plays an important role in maintaining RPE integrity. Mutations in this gene cause BCD, a group of ad pattern dystrophies of the RPE with an age at onset between 14 and 55.17 In addition, the mouse model also exhibits the same ocular features as the human patients.17 In this study, a likely disease-causing variant, p.Gly353Cys, in the CTNNAI gene was detected in patient LCATH7, who was diagnosed with isolated LCA at the age of 5 months (Table 1). This patient developed rapid and severe visual loss, which differs from previous studies in which patients with BCD would experience a gradual loss of vision that is usually only apparent in old age. Although there was absence of cosegregation analysis in the patient’s father, he has no symptoms of the disease. The glycine residue 353 of catenin alpha 1 is conserved among vertebrates. Based on the HOPE server, the p.Gly353Cys variant is predicted to alter protein conformation and will disturb the local structure. Additionally, the p.Gly353Cys variant was not found in the screening of 260 ethnically matched control chromosomes and all publicly available databases. In addition to the heterozygous CTNNAI missense variant, a novel heterozygous variant, p.Pro1805Leu, was also identified in the KIAA1549 gene associated with autosomal recessive RP. Because this variant was found on only one allele and known variant in this gene has never been reported to modify the phenotype along with other genes, thus the p.Pro1805Leu in KIAA1549 gene was classified as a VUS. However, based on current knowledge, we cannot exclude the possibility that this heterozygous missense KIAA1549 allele may have some modifying effects on the phenotypic expression of the patient (LCATH7) to be early onset at birth which is different from previously reported patients with CTNNAI mutations.17 From all of these data, we demonstrate for the first time that a heterozygous variant in the CTNNAI gene can lead to LCA with the fundus findings similar to Bspd.

Mutations in the CYP4V2 gene are responsible for triggering BCD, a rare autosomal recessive disease with variable phenotypic features. The disease usually presents between the second and fourth decades. Severe visual impairment is observed by the fifth or sixth decades of life.16 The CYP4V2 gene encodes a member of the cytochrome P450 superfamily, which may play a role in fatty acid homeostasis in the eye.23 The CYP4V2 mutations can cause not only BCD but also RP.25 Patient LCATH8, a 2-year-old male born to consanguineous parents, carried compound heterozygous missense mutations in the CYP4V2 gene. These identical mutations have also been reported in a BCD patient from a consanguineous family.16 However, the clinical manifestations were so different in that our patient developed symptoms very early in life. These results are consistent with previous reports showing that the same mutation in the CYP4V2 gene can cause

Table 2. Pathogenic Variants Identified in This Study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gene</th>
<th>MOI</th>
<th>Diagnosis</th>
<th>Chr</th>
<th>Exon</th>
<th>DNA Change</th>
<th>Protein Change</th>
<th>Zygosity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCATH1</td>
<td>CEP290</td>
<td>ar</td>
<td>LCA</td>
<td>12</td>
<td>6</td>
<td>c.367C&gt;T</td>
<td>p.Gln123Ter</td>
<td>Heterozygous</td>
<td>Novel</td>
</tr>
<tr>
<td>LCATH2</td>
<td>IQCB1</td>
<td>ar</td>
<td>LCA</td>
<td>3</td>
<td>10</td>
<td>c.945A&gt;T</td>
<td>p.Ile515Ter</td>
<td>Heterozygous</td>
<td>Novel</td>
</tr>
<tr>
<td>LCATH3</td>
<td>NMNAT1</td>
<td>ar</td>
<td>LCA</td>
<td>1</td>
<td>5</td>
<td>c.196C&gt;T</td>
<td>p.Arg661Trp</td>
<td>Heterozygous</td>
<td>Reported12</td>
</tr>
<tr>
<td>LCATH4</td>
<td>RPGRIP1</td>
<td>ar</td>
<td>LCA</td>
<td>14</td>
<td>9</td>
<td>c.1111C&gt;T</td>
<td>p.Arg371Ter</td>
<td>Homozygous</td>
<td>Reported14</td>
</tr>
<tr>
<td>LCATH5</td>
<td>ALMS1</td>
<td>ar</td>
<td>AS</td>
<td>2</td>
<td>8</td>
<td>c.3896C&gt;A</td>
<td>p.Ser1299Ter</td>
<td>Homozygous</td>
<td>Reported15</td>
</tr>
<tr>
<td>LCATH6</td>
<td>ALMS1</td>
<td>ar</td>
<td>AS</td>
<td>2</td>
<td>8</td>
<td>c.3896C&gt;A</td>
<td>p.Ser1299Ter</td>
<td>Homozygous</td>
<td>Reported15</td>
</tr>
<tr>
<td>LCATH7</td>
<td>CTNN1</td>
<td>ad</td>
<td>LCA</td>
<td>5</td>
<td>7</td>
<td>c.1057G&gt;T</td>
<td>p.Gly353Cys</td>
<td>Heterozygous</td>
<td>Novel</td>
</tr>
<tr>
<td>LCATH8</td>
<td>CYP4V2</td>
<td>ar</td>
<td>LCA</td>
<td>4</td>
<td>2</td>
<td>c.257G&gt;T</td>
<td>p.Glu79Asp</td>
<td>Heterozygous</td>
<td>Reported16</td>
</tr>
</tbody>
</table>

Nucleotide numbering reflects cDNA numbering with position 1 corresponding to the "A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (in the public domain, http://www.hgvs.org/mutnomen). The initiation codon is codon 1. The nucleotide position of each gene was based on these GenBank cDNAs (accession number): ALMS1 (NM_001903.4), CEP290 (NM_025114.3), CTNN1 (NM_001905.3), CYP4V2 (NM_207352.3), IQCB1 (NM_001023570.3), NMNAT1 (NM_022787.5), and RPGRIP1 (NM_020566.5). MOI, mode of inheritance; Chr, chromosome.
distinctly different clinical manifestations in BCD patients and RP patients. Phenotypic variability between these patients may be due to the effect of modifier genes or epigenetics. In addition to the two CYP4V2 mutations, a novel single heterozygous nonsense variant, p.Arg3607Ter, in the ALMS1 gene associated with an arAS has also been identified. It is possible that this ALMS1 variant may act as an extra allele affecting the LCATH8 patient’s genome as a modifying factor leading to more severe phenotype (infancy onset) that was caused by CYP4V2 mutations of which most phenotypes such as BCD and RP are adult onset. This is the first time to report that CYP4V2 mutations were not only responsible for BCD and RP, but also for LCA. Because an abnormality in serum fatty acid concentration was observed in BCD patients, fatty acid concentration was observed in BCD patients, and also for LCA. Because an abnormality in serum fatty acid concentration was observed in BCD patients, it is required to confirm the association between the CTNNA1 and CYP4V2 genes and LCA.

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