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Case Report

# Identification of a Nonsense Mutation in AIPL1 Gene Causing Leber Congenital Amaurosis in a Family Clinically Diagnosed as Retinitis Pigmentosa

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## Abstract

Leber congenital amaurosis is a rare inherited retinopathy resulting in severe vision loss at an early age. We present a family wherein leber congenital amaurosis was clinically misdiagnosed as retinitis pigmentosa in a pregnant women with a clinically documented family history of retinal dystrophy. Clinical exome study in the proband identified a nonsense variant (c.834 G>A / p.W278X) in the *AIPL1* gene. A prenatal study from the chorionic villus found the foetus to be heterozygous for the identified variant, confirming the carrier status. This study highlights the utility of advanced genomic diagnosis for the phenotypically overlapping ophthalmic disorders.

**Keywords**: Leber Congenital Amaurosis; Genetics; Retinitis Pigmentosa; Prenatal Diagnosis

## Introduction

Leber congenital amaurosis (LCA) is a rare congenital retinopathy with an estimated prevalence of 1:50,000 - 1:100,000, with 19 responsible genes identified till date [1,2]. It results in severe retinopathy with an early age of onset [3]. Clinically LCA consists of severe visual loss near or at birth, nystagmus, amaurotic pupils, and pigmentary retinopathy. Retinitis Pigmentosa (RP) is also a retinal dystrophy consisting of progressive severe loss of visual acuity, pigmentary retinopathy, and nystagmus. It may be categorized as: aplasia with abnormal embryological photoreceptor formation, degeneration with progressive photoreceptor cell death, or dysfunction with lack of key biochemicals [4]. This symptom overlap can lead to a clinical misdiagnosis of LCA, emphasizing the need for genetic diagnostics. Multiple cases have been reported where a genetic analysis corrects a clinical misdiagnosis, which can assist in counselling and further prevention of the disease [5,6]. Genetic disorders are amplified in a country like India, where consanguineous and endogamous marriages are common [7]. To highlight the importance of accurate diagnoses in phenotypically overlapping disorders, we present the following family where a patient with severely decreased visual acuity and pigmentary retinopathy, clinically diagnosed with RP, was referred for prenatal testing for her fetus.

## Case Study

A 23-year old female, consanguineously married, 3 months pregnant (primigravidae) was referred by a fetal medicine expert for a prenatal diagnosis. The female was clinically diagnosed with RP, having several affected family members clinically diagnosed with RP (Figure 1). The husband had no previous history of any associated disorder, while the female had 3 unaffected brothers and one affected sister. The husband of the proband was her maternal uncle. A total of 5 out of 25 members of the proband's family, including herself were clinically diagnosed with RP. The proband's parents did not have a consanguineous marriage but her maternal aunt was diagnosed with RP, confirming that the pathogenic gene was present in the maternal family. The proband's father can be clinically established to be a carrier, as 2 of the 5 offspring are affected but were not available for the present study. The proband's husband was normal, having one affected sister, who is the mater-

nal aunt of the proband. Blood samples of the proband, her husband, unaffected brother, and a chorionic villus sample of the fetus were analyzed.

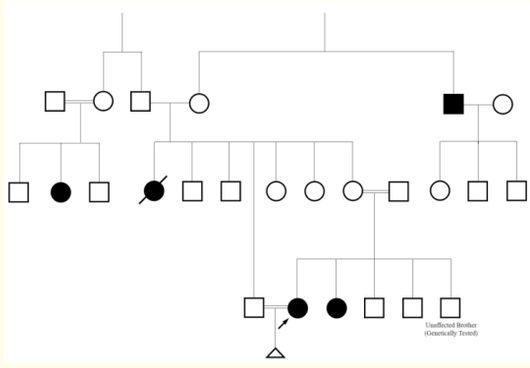


**Figure 1:** Pedigree chart of the Family.

The proband had diminished vision since birth with several of her family members affected with a similar phenotype. Her first clinical visit was during her third month of pregnancy when she was 23 years old; without any prior history of counselling or treatment. A fundus examination showed bilateral optic disc pallor, with retinal artery attenuation. Bony spicule-like pigments were present in the mid-periphery and posterior pole of the fundus. Visual acuity testing found the patient had an inaccurate perception of light in her left eye, with perception of light in her right eye. Nystagmus was present in the right eye. The intra-ocular pressure was normal in both eyes. There were no other clinically spectacular findings.

The first trimester ultrasound showed no sonographically detectable anomalies in the fetus.

Clinical exome study was carried out in the proband covering 8400 genes by Next Generation sequencing (NGS) using the Illumina Hiseq platform with 100x coverage of all the genes related to retinal degeneration. She was homozygous for the variant c.834 G>A in exon 6 of the *AIPL1* (OMIM #604393) gene, associated with autosomal recessive LCA (Figure 2A). Further confirmation of the variant was carried out in the proband, unaffected brother and the unaffected husband. This has identified heterozygous variant c.834 G>A in her unaffected brother and wild type in the husband. The fetus in an ongoing study showed heterozygous status for the above mentioned *AIPL1* variant suggesting a carrier status and had delivered a healthy child with a full-term normal delivery (Figure 2B-2D).

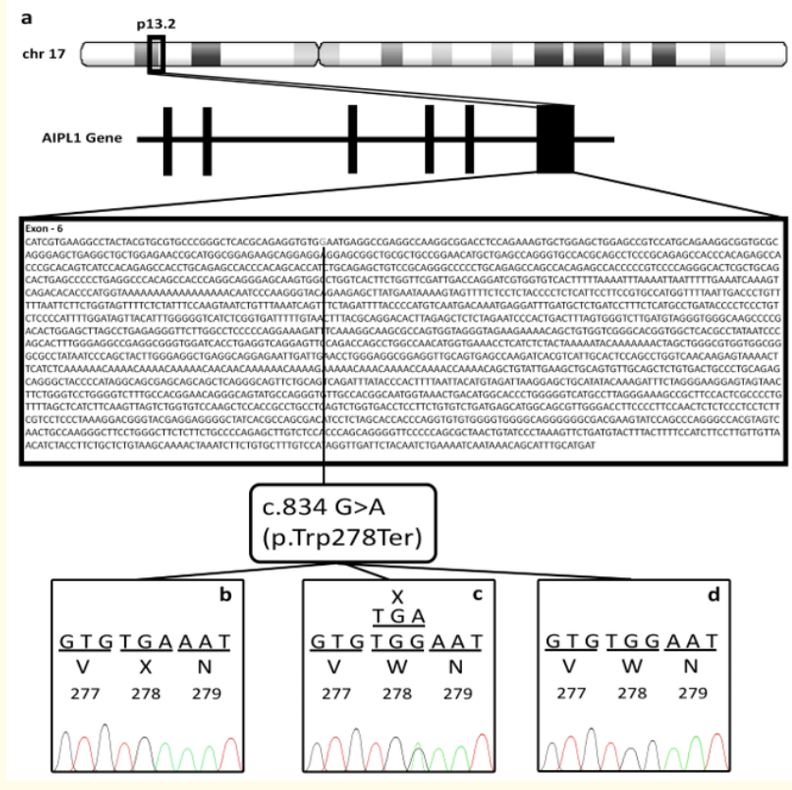


**Figure 2:** Molecular genetic analysis (a) Schematic presentation of AIPL1 gene position on chr17p13.2 and reported homozygous variant c.834 G>A (p.Trp278Ter) in AIPL1 gene (b) Sequence chromatogram of affected female (homozygous c.834 G>A (p.Trp278Ter) in AIPL1 gene (c) Sequence chromatogram of fetus (heterozygous c.834 G>A (p.Trp278Ter) in AIPL1 gene) (d) Sequence chromatogram of husband (wild type AIPL1 gene)


**Supplementary Figure 1:** Result of clinical exome study using next generation sequencing (NGS) using the Illumina Hiseq platform, identifying the specified variant.

## Discussion

Our study identifies a previously known nonsense mutation in AIPL1 gene as a cause of LCA in 2002 by Sohocki., *et al*. clinically LCA consists of severe visual loss near or at birth, nystagmus, amaurotic pupils and pigmentary retinopathy. The visual acuity ranges from 20/200 to perception of light, and very rarely no perception of light [4]. The visual impairment is stable or very slowly progressive. This is in concordance with the case under our study. Associated features include the oculodigital sign of Franceschetti, ptosis, strabismus, hyperopia, cataracts, keratoconus/globus, an undetectable/reduced electroretinogram and retinal vascular attenuation, of these later was identified in our case.

### Differential diagnosis

Some multi-system syndromes may present with early-onset retinal dystrophy, however LCA usually occurs without any systemic involvement. For example, Senior Loken Syndrome also presents with Juvenile nephronophthisis, while Conorenal syndrome patients present with cerebellar hypoplasia and cone-shaped digital epiphyses, and Joubert syndrome also presents with cerebellar vermis hypoplasia, ataxia and intellectual disability [4]. None of these signs were present in our case. Achromatopsia, incomplete achromatopsia, complete congenital stationary night blindness (CSNB), and incomplete CSNB also present with congenital blindness and nystagmus. Patients with achromatopsia have blepharospasm in the presence of light, while CSNB patients can see well during the day [4]. Patients of LCA do not see well at either day or night, however one subtype (*RPE-65* genotype) have night blindness and prefer the day [2]. RP consists of all retinal dystrophies with loss of photoreceptor cells and retinal pigment deposits. A fundus examination in both RP and LCA can show pigmentary deposits resembling bone spicules, along with attenuation of retinal

vessels [8]. Hence, clinical signs can point to both LCA and RP in this case.

## Molecular genetic study

LCA follows an autosomal recessive pattern of inheritance, and rarely autosomal dominant [9]. Carriers do not present with any symptoms, except for some cases of *GUCY2D* mutations [10]. The visual acuity of patients with LCA varies widely, with different genes mutations responsible for different levels of visual impairment. *AIPL1* mutations are associated with severely decreased visual acuity in the first year of life, while *RPE65* mutations have progressive loss [3]. Our case was genetically and clinically suggestive of LCA as she had a severe decreased visual acuity early in her childhood.

LCA accounts for 10 - 20% of all childhood blindness, and 5% of all inherited retinal diseases. LCA has not been well studied in India, with a relatively small number of mutations being identified [11]. Only 74 mutations have been found in LCA patients in India till date (Table 1). The variant found in this case was first identified in a study in 2000, in families of both Pakistani and European descent. Considering the large geographical range and close proximity to India, there is a probability for this variant to be prevalent in the Indian population.

| Gene | Mutation | Change in Protein | Study Author |
|---|---|---|---|
| RPE65 | 1409C>T | p.(Pro470Leu) | G Mamatha., *et al*. |
| RPE65 | c.963T>G | p.(Asn321Lys) | |
| RPE65 | c.858+1G>T | | S Sundaramurthy., *et al*. |
| CRB1 | c.3770G>A | | |
| GUCY2D | c.994delC | | |
| AIPL1 | c.834G>A | p.(Trp278*) | Present Study (Sheth., *et al*.) |
| RPE65 | c.1409C>T | p.(Pro470Leu) | |
| AIPL1 | c.613_622 delATCATCTGCC | | |
| MERTK | c.721C>T | p.(Val272Met) | |
| RPGRIP1R DH12 | c.344-8C>T | | |
| RPE65 | c.1056 G>A | | A Verma., *et al*. |
| RPE65 | c.1338+20A>C | | |
| *RPE65 | c.868C>T | p.(His290Tyr) | |
| AIPL1 | c.268G>C | p.(Asp90His) | |
| AIPL1 | c.286G>A | p.(Val96Ile) | |
| GUCY2D | c.61T>C | p.(Trp21Arg) | |
| GUCY2D | c.154G>T | p.(Ala52Ser) | |
| GUCY2D | c.2101C>T | p.(Pro701Ser) | |
| GUCY2D | c.2345T>A | p.(Leu782His) | |
| RPGRIP1 | c.574A>G | p.(Lys192Glu) | |
| RPGRIP1 | c.907-17 del TAA | | |
| RPGRIP1 | c.3097 G>C | p.(Glu1033Gln) | |
| RPGRIP1 | c.3560_3566 del 7bp | p.(Gly1188Arg_1189delPheSer) | |
| RPGRIP1 | c.1639G>T | p.(Ala547Ser) | |
| CRB1 | c.3307G>A | p.(Gly1103Arg) | S Srilekha., *et al*. |
| IQCB1 | c.1278+6T>A | p.(Gln378Alafs*2) | |
| RPE65 | c.1102T>C | p.(Tyr368His) | P Sundaresan., *et al*. |
| RPE65 | c.814C>T | p.(Gly272Arg) | N Srikrupa., *et al*. |
| AIPL1 | c.247G>A | p.(Glu83Lys) | |
| AIPL1 | c.689A>G | p.(Asn230Ser) | |
| AIPL1 | c.844G>T | p.(Glu282*) | |
| AIPL1 | c.910G>T | p.(Glu304*) | |

| | | | |
|---|---|---|---|
| CRB1 | c.1073ins | p.(Ser359Glufs* 20) | |
| CRB1 | c.4005+1 G>A | r.spl? | |
| CRB1 | c.4168C>T | p.(Arg1390*) | |
| CRX | c.122G>A | p.(Arg41Gln) | |
| GUCY2D | c.524T>G | p.(Leu175Arg) | |
| GUCY2D | c.839C>G | p.(Thr280Arg) | |
| GUCY2D | c.1790G>A | p.(Gly597Glu) | |
| GUCY2D | c.1978C>T | p.(Arg660*) | |
| GUCY2D | c.2062G>A | p.(Gly688Arg) | |
| GUCY2D | c.2182G>A | p.(Asp728Asn) | |
| GUCY2D | c.2663delG | p.(Gly888Alafs*) | |
| GUCY2D | c.2885delC | p.(Thr962Ilefs*) | |
| GUCY2D | c.3037G>A | p.(Gly1013Arg) | |
| GUCY2D | c.3065T>A | p.(Leu1022*) | |
| GUCY2D | c.3118C>G | p.(Arg1040Gly) | |
| IQCB1 | c.994C>T | p.(Arg332*) | |
| IQCB1 | c.1333C>T | p.(Arg445*) | |
| IQCB1 | c.1363C>T | p.(Arg455*) | |
| IQCB1 | c.1558C>T | p.(Gln520*) | |
| LCA5 | c.838C>T | p.(Arg280*) | |
| LCA5 | c.955G>A | p.(Ala319Thr) | |
| LCA5 | c.1062_ | p.(Tyr354*) | |
| LCA5 | c.1422delT | p.(Ile474Metfs*) | |
| LCA5 | | p.(Tyr354*) | |
| NMNAT1 | c.53A>G | p.(Asn18Ser) | |
| NMNAT1 | c.109G>A | p.(Gly37Arg) | |
| RD3 | c.296+1 G>A | | |
| RDH12 | c.146C>T | p.(Thr49Met) | |
| RDH12 | c.184C>T | p.(Arg62*) | |
| RDH12 | c.746G>T | p.(Arg249Leu) | |
| RPE65 | c.46_49 delTTTG | p.(Phe16Lysfs* 14) | |
| RPE65 | c.353+1 G>T | | |
| RPE65 | c.361dupT | p.(Ser121Phefs* 10) | |
| RPE65 | c.1109T>A | p.(Leu370His) | |
| RPE65 | c.1514T>G | p.(Leu505Arg) | |
| RPGRIP1 | c.895G>T | p.( Glu299*) | |
| RPGRIP1 | c.2041C>T | p.(Gln681*) | |
| RPGRIP1 | c.3434delA | | |
| RPGRIP1 | c.3788T>C | p.(Leu1263Pro) | |
| SPATA7 | c.18A>G | | |
| SPATA7 | c.1215+5 C>A | r.1161_1215del | |
| TULP1 | c.1047T>G | p.(Asn349Lys) | |

**Table 1:** Mutation spectrum of LCA in India.

Mutations found in the AIPL1 gene account for 11% of the mutations known to cause LCA in India. The AIPL1 gene is expressed in both photoreceptors and the pineal gland. The protein is present in photoreceptor inner segments and synaptic terminals and is associated with protein trafficking. Its interaction with several other proteins is facilitated through its tetratricopeptide repeat domains. Specifically, it binds to farnesylated proteins (DNAJA2, gamma-transducin, NUBI) [13]. These are essential for photoreceptor structure. The protein formed as a result of this mutation forms SDS-insoluble cytoplasmic inclusions, which suggest that it undergoes misfolding and aggregating due to it being non-functional [14]. This can explain why mutations in the AIPL1 gene can lead to loss of photoreceptor function. Most patients with mutations in the AIPL1 gene have a visual acuity of only light perception by the time they reach the second decade of their life. The variant c.834 G>A may contribute to up to 48% of the alleles causing AIPL1 dysfunction and is relatively common in North America [15].

19% of LCA mutations in India are mutations of the RPE65 gene. Mutations in this gene are concentrated in Southern India specifically, which may be due to increased consanguineous marriages [16]. In patients in India with IQB1 mutations, there is a risk of developing renal abnormalities, with a highly variable rate of onset. Hence Senior Loken syndrome may be misdiagnosed as LCA if proper genetic testing is not carried out [17]. Patients in India with GUCY2D gene mutations rarely showed optic disc pallor but had a characteristic feature of a greyish tapetal reflex and minimal peripheral retinal pigment epithelium granularity [11].

Unfortunately, there is no treatment for LCA. Human gene therapy trials using the rAAV2/2 *RPE65* vector have shown promise for potential treatment of the disease [18-20]. However, these remain in the initial phases of testing, and cost may prove to be a barrier. In developing countries like India, prevention of the disease if the only viable solution, thus making genetic testing essential. However, in many studies up to 39% of cases may not be associated with a known gene mutation [11]. Mutations in unscreened intronic regions or in regulatory regions may be responsible for such cases.

Thus, advanced genetic investigations by NGS in the proband has corrected the clinical diagnosis of RP and based on this precise genetic counseling was provided leading to a healthy unaffected baby in the subsequent pregnancy. It is imperative that utilization of advanced genomic study by ophthalmologists will be able to offer precise genetic counseling and its prevention in subsequent pregnancy thereby lessening the burden of an inheritable and incurable ophthalmic disorder. This also save the family from psychological trauma and financial burden in the management of the diseases.

## Key Message

The advent of accessible genetic diagnostics must be utilized by clinicians in creating accurate diagnoses in ophthalmic practice for further prevention of the disease and precise counseling.

## Ethics Approval

A written informed consent was obtained from parent and ethical committee approval was obtained from the institutional ethics committee approval as per Helsinki declaration.

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