A Novel PRPF31 Mutation in a Large Chinese Family with Autosomal Dominant Retinitis Pigmentosa and Macular Degeneration

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Abstract

**Purpose:** This study was intended to identify the disease causing genes in a large Chinese family with autosomal dominant retinitis pigmentosa and macular degeneration.

**Methods:** A genome scan analysis was conducted in this family for disease gene preliminary mapping. Snapshot analysis of selected SNPs for two-point LOD score analysis for candidate gene filter. Candidate gene PRPF31 whole exons' sequencing was executed to identify mutations.

**Results:** A novel nonsense mutation caused by an insertion was found in PRPF31 gene. All the 19 RP patients in 1085 family are carrying this heterozygous nonsense mutation. The nonsense mutation is in PRPF31 gene exon9 at chr19:54629961-54629961, inserting nucleotide “A” that generates the coding protein frame shift from p.307 and early termination at p.322 in the snoRNA binding domain (NOP domain).

**Conclusion:** This report is the first to associate PRPF31 gene’s nonsense mutation and adRP and JMD. Our findings revealed that PRPF31 can lead to different clinical phenotypes in the same family, resulting either in adRP or syndrome of adRP and JMD. We believe our identification of the novel “A” insertion mutation in exon9 at chr19:54629961-54629961 in PRPF31 can provide further genetic evidence for clinical test for adRP and JMD.

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Introduction

Retinitis pigmentosa (RP) and macular degeneration (MD) are a clinically and genetically heterogeneous group of retinal dystrophies characterized by the progressive degeneration of photoreceptors, eventually resulting in severe visual impairment or blindness [1]. RP and MD are typically characterized as types of rod-cone dystrophy that are caused by the cell death of rod and cone photoreceptors. RP is characterized by a loss of peripheral vision, whereas MD is characterized by a loss of central vision. RP can be divided into autosomal dominant, autosomal recessive, and X-linked hereditary types [2]. The global incidence of RP is about 1/3,500, and more than 100 million people are affected worldwide [3]. MD can have a dominant or recessive inheritance pattern. MD or age-related macular degeneration (AMD) is a leading cause of vision loss in those over the age of 55 years. Juvenile macular degeneration (JMD) is a rare disease that causes central vision loss, often beginning in childhood or young adulthood. Forms of JMD include Best disease, Stargardt’s disease, and juvenile retinoschisis [4]. Until now, there have been no effective measures for RP and MD prevention and treatment.

Autosomal dominant RP (adRP) is a common inheritance model of RP. Thus far, 19 loci, including 18 genes, have been identified as adRP-causing genes (RetNetweb site, https://sph.uth.edu/retnet/sum-dis.htm); they are BEST1 (11q12.3), CAT (17q23.2), CRX (19q13.32), FSCN2 (17q25.3), GUC1A1B (6p21.1), IMPDH1 (7q32.1), KIFL7 (7p15.3), NR2E3 (15q23), NPHP2 (15q12.1), NPHP3 (1q21.2), PDE6B (20q13.33), PDE7B (17p13.3), PRPF31 (19q13.42), PRPH2 (6p21.1), RHOD (3q21.1), ROM1 (11q12.3), RPE1 (8q12.1), RPE65 (17q23.2), and RPE67 (17q21.2).
Among these genes, RHO and PRPF31 are the genes in which mutations are most commonly found in the Chinese population. In the RetNet database, there are also 26 loci, including 23 genes have been identified as being involved in autosomal recessive RP: (arRP) ABCA4, BEST1, C2ORF71, C8orf37, CERKL, CLRN1, CNGA1, CGB1, CRB1, DHDDS, EYS, FAM161A, IDH3B, IMPG2, LRAT, MAK, MERTK, NR2e3, NRL, PDE6A, PDE6B, PDE6G, PRCD, PROM1, RBP3, RGR, RHO, RLBP1, RP1, RPE65, SAG, SPATA7, TTC3, TULP1, USH2A, and ZNF513). Five loci, including three genes (OFD1, RP2, and RPGR), have been identified as being involved in X-linked RP.

Figure 1. The pedigree of the family 1085, with autosomal dominant retinitis pigmentosa. Normal individuals are shown as clear circles (female) or squares (male), and affected individuals are shown as solid symbols. Patients with fovea centralisareflexia are highlighted in red. This family contains six generations in total (shown in Roman numerals). Individuals with the PRPF31 gene mutation in the form of incomplete penetrance are shown in green (samples 5, 42, 46, and 56).

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There are eleven genes that have been identified as being involved in autosomal dominant MD (adMD) (RetNet website), including \textit{BEST1}, \textit{C1QTNF5}, \textit{EFEMP1}, \textit{ELOVL4}, \textit{GUCA1B}, \textit{HMCN1}, \textit{PROM1}, \textit{PRPH2}, \textit{RP1L1}, and \textit{TIMP3}. Two genes, \textit{ABCA4} and \textit{CFH}, have been identified as being involved in autosomal recessive MD (arMD); \textit{RPGR} have been identified as being involved in X-linked MD. In addition, genes \textit{ABCA4}, \textit{ARMS2}, \textit{C2}, \textit{C3}, \textit{CFB}, \textit{CFH}, \textit{ERCC6}, \textit{FBLN5}, \textit{HMCN1}, \textit{HTRA1}, \textit{RAX2}, \textit{TLR3}, and \textit{TLR4} are associated with AMD.

In this study, we reported on a disease-causing gene in a large Chinese family 1085. In this family, 19 patients showed typical clinical symptoms of RP. Among these, five subjects showed RP syndrome and mild MD.

Materials and Methods

Ethics Statement

This project was approved by the ethics committee of the hospital of Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China. Informed consent was obtained from all patients and family members involved in this study. A written informed consent was obtained from each participant.

Patient Recruitment

The 1085 family members with adRP were collected from Sichuan province. Family members were clinically diagnosed at the Sichuan Provincial People’s Hospital. Peripheral blood samples of index cases and their family members were collected in EDTA tubes. Genomic DNA was extracted from peripheral blood by using the standard genomic DNA extraction method.

Genetic Analysis

\textbf{Linkage analysis.} Genome-wide screening was conducted using Linkage analysis chip01 (illumina) according to the protocol. All 1085 family samples were screened. Data set was analyzed using LINKAGE package.

\textbf{Snapshot analysis.} Seven SNPs around gene \textit{PRPF31} were selected for Snapshot analysis for fine chromosomal localization. The procedure of Snapshot analysis was carried out according to ABI PRISMSNaPshotTM MultiplexKit protocol, and the processed samples were analyzed via an ABI 3130XL genetic analyzer.

\textbf{Sanger sequencing analysis.} To find mutations in the disease candidate gene, we used sanger sequencing analysis. The procedure was carried out according to the ABI BigDye sequencing protocol, and the processed samples were sequenced via an ABI3130XL genetic analyzer.
### Table 1. Features of the 1085 pedigree patients.

| Subject   | Gender | Age | Height (cm) | Weight (kg) | On-set of RP | Present VA | clinical symptoms                          |
|-----------|--------|-----|-------------|-------------|--------------|------------|--------------------------------------------|
| 1085-03   | Male   | 82  | 173         | 65          | child        | <<0.1      | RP, bilateral cataract                      |
| 1085-08   | female | 13  | 139         | 26          | child        | <<0.1      | RP                                         |
| 1085-09   | Male   | 15  | 144         | 32          | child        | <<0.1      | RP                                         |
| 1085-11   | Male   | 19  | 170         | 55          | child        | 0.2/0.3    | RP                                         |
| 1085-12   | female | 19  | 163         | 50          | child        | <<0.1      | RP                                         |
| 1085-13   | Male   | 41  | 174         | 81          | child        | <<0.1      | RP                                         |
| 1058-14   | female | 43  | 160         | 57          | child        | 0.3/0.3    | RP, bilateral cataract                      |
| 1085-15   | Male   | 51  | 174         | 50          | child        | 0.4/0.6    | RP, fovea centralis areflexia, bilateral cataract |
| 1085-22   | Male   | 65  | 178         | 58          | 48           | <<0.1      | RP, fovea centralis areflexia              |
| 1085-25   | female | 43  | 152         | 67          | child        | <<0.1      | RP, bilateral cataract                      |
| 1085-26   | female | 68  | 159         | 50          | child        | <<0.1      | RP, bilateral cataract                      |
| 1085-27   | Male   | 17  | 165         | 45          | child        | <<0.1      | RP                                         |
| 1085-30   | female | 53  | 158         | 65          | child        | 0.2/0.3    | RP                                         |
| 1085-32   | female | 55  | 160         | 43          | child        | 0.1/0.1    | RP, bilateral cataract                      |
| 1085-33   | Male   | 46  | 177         | 74          | child        | 0.5/0.5    | RP                                         |
| 1085-36   | Female | 39  | 165         | 51          | child        | <<0.1      | RP, fovea centralis areflexia              |
| 1085-38   | Female | 21  | 170         | 55          | child        | <<0.1      | RP, fovea centralis areflexia, JMD          |
| 1085-39   | Male   | 35  | 180         | 90          | 8 to 9       | N          | RP                                         |
| 1085-43   | Female | 37  | 160         | 60          | child        | N          | RP, fovea centralis areflexia              |

### Table 2. Primers used for Snapshot analysis.

| SNP          | Primer                  | Size  |
|--------------|-------------------------|-------|
| rs4806711    | F ACGTGAGTCCCTTCTCTCT   | 506bp |
|              | R GGGGAACCCCCGTCTCTCT   |       |
| Snapshot primer | AGGAGGATGTGATGATGATGG |       |
| rs56220912   | F GCCAACCAGCAGTCTACC    | 504bp |
|              | R CCTCTCAAGCTCTCTCCTC   |       |
| Snapshot primer | GCTCACTCTCGAGCCCCCTC   |       |
| rs10424816   | F GGGCGCTTTTTTCTCTTG    | 423bp |
|              | R GTTCACTGAACCTCGCTCT   |       |
| Snapshot primer | CTAGGTCTCGC TGTGGAAGATCATGAACCTACTG    |       |
| rs254271     | F GGCTGAAGTCAAGGTGTG    | 407bp |
|              | R ACAGATCCTGTGTGGAAGG    |       |
| Snapshot primer | TGCTCTCTGTCCTCATATC    |       |
| rs8109631    | F CCCAGATTTTGAGCTACAG   | 428bp |
|              | R AGGGCTTCTCCCCAGTATGA  |       |
| Snapshot primer | CAATCAGATGATCATCAATATGTGCAAAG |       |
| rs465169     | F ACCCAACCTCACCTTACCTC  | 500bp |
|              | R GCTGTGTCTCTGAGGCCCCCTC |       |
| Snapshot primer | GCTCCCTCGGCTCCCGCTCTCTAACCACAGGCTGCTCTT |       |
| rs36633      | F AAGAGACAGCCCCAGTCT    | 523bp |
|              | R TTGTGTTTGTAGGCCCCCTC  |       |
| Snapshot primer | CAGTCATGCTGCAACAGCTGATGACTGGGATGGAGGAGATGATTAGCCTGGA |       |

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Clinical diagnosis

Ophthalmic examinations were executed, including of visual acuity, intraocular pressure, ocular motility, pupillary reaction, slit-lamp examination, dilated fundus examination and visual electrophysiological testing. SD-OCT was examined using SPECTRALIS® platform (Heidelberg engineering, Germany). mfERG was detected using RetIscan (Roland instruments, Germany).

Results

Clinical Manifestations of Members of the Pedigree

In this six-generation pedigree 1085, 65 members consented to participate in this study (Fig. 1). Nineteen individuals of the 1085 family were considered to be affected by RP, and 46 individuals were considered to be unaffected. A fundus examination of the patients showed typical RP features, including peripheral vision loss, night blindness, optic disk atrophy, retinal vascular stenosis, pigmentation, and the severe reduction or extinguishing of ERG. For example, typical pigmentation can be seen on the retina of patient 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods.

Mutation Screening and SNP Genotyping Results

First, via genome-wide scan and Linkage analysis, rs9788, rs8109631, rs465169, rs36633, and rs8111838 in 19q13.42 were considered to be unaffected. A fundus examination of the patients showed typical RP features, including peripheral vision loss, night blindness, optic disk atrophy, retinal vascular stenosis, pigmentation, and the severe reduction or extinguishing of ERG. For example, typical pigmentation can be seen on the retina of subject 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G). Similar fovea centralisareflexia phenotype can be found in patients 15, 22, 36 and 43. For example, patient 15, both his right eye and left eye in macaia showed attenuation by SD-OCT examination (Fig. 2 H–M) and he has very low light stimulus reaction by mfERG examination (Fig. 2 N), especially in his right eye. Patients with fovea centralis areflexia are highlighted in red in Fig. 1. In addition to JMD, subjects 3, 14, 15, 25, 26, and 32 showed bilateral cataract via by slit lamp examination. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G). Similar fovea centralis areflexia phenotype can be found in patients 15, 22, 36 and 43. For example, patient 15, both his right eye and left eye in macaia showed attenuation by SD-OCT examination (Fig. 2 H–M) and he has very low light stimulus reaction by mfERG examination (Fig. 2 N), especially in his right eye. Patients with fovea centralis areflexia are highlighted in red in Fig. 1. In addition to JMD, subjects 3, 14, 15, 25, 26, and 32 showed bilateral cataract via by slit lamp examination. The detailed information on the affected patients is shown in Table 1.

Table 3. Two-point LOD scores around disease causing gene PRPF31.

| SNP | Location (chr19) | θ = 0 | θ = 0.1 |
|-----|------------------|-------|---------|
| rs4806711 | 54619191 | −2.24939 | 0.537837 |
| rs56220912 | 54626055 | 1.750628 | 1.44181 |
| rs10424816 | 54630208 | 1.69589 | 2.641756 |
| rs254271 | 54630757 | −0.78082 | 1.591041 |
| rs8109631 | 54080144 | 1.190325 | 2.612824 |
| rs465169 | 54526970 | 0.598506 | 2.773549 |
| rs36633 | 54646288 | 1.531824 | 1.285244 |

Table 4. Primers used for PRPF31 whole exons sequencing.

| Exon | Primer | Size |
|------|--------|------|
| Exon1 F | AGTTTCCGTGGTTCCGCTTC | 437bp |
| Exon2 F | TTTGTCGGGGCAAGTTTTTA | 300bp |
| Exon3 F | TAGCAGGGGCTCTAGACAG | 203bp |
| Exon4 F | CAGGAGGGGTTAGGGATTTA | 214bp |
| Exon5 F | AAGAGGAAGAGGGACATGGGAAAG | 214bp |
| Exon6 F | AGGAGGTCTAGCTAACAGAGAAGAAGGAAG | 250bp |
| Exon7 F | CAGGTTCGACACGACCAACAACAACAACAAC | 432bp |
| Exon8 F | TACTCACCCCCACTCTCTG | 299bp |
| Exon9 F | CGTTTCGTTTCTGTTACCT | 209bp |
| Exon10 F | TTTAACTAAGAGCCTGGGATATCT | 267bp |
| Exon11 F | GGTAGGATGTTTAGGGCAT | 250bp |
| Exon12 F | TTAGCTGAGGAGGAGGGCT | 207bp |
| Exon13 F | ACCAGAGGAGAACAGAGGAG | 207bp |
| Exon14 F | GCCCTCTGATGGGTACAGATTT | 514bp |
| Exon15 F | CCGGCTGATTGGAAAAATGAT | 514bp |

In our pedigree, we found one novel mutation in a large adRP family. Primers designed to amplify all 14 exons and flanking regions of PRPF31 from the genomic DNA are shown in Table 4. We found that a novel heterozygous insertion in exon9 at chr19:54629961-54629961 (UCSC:feb.2009 (GRCH37/ HGI190)) that inserted an “A” nucleotide was co-segregated between patients and normal members (Figure 3AB). Mutations can be detected in all the affected samples. However, this mutation can also be detected in normal samples 5, 42, 46, and 56, showing partial penetrance (Figure 1 in green). This nonsense mutation leads to a protein frame shift from p.307 and early termination at p.322 in the snoRNA binding domain (NOP domain) (Figure 3C).

Discussion

In our pedigree, we found one novel PRPF31 mutation in a large adRP family. In this family, subject 38 showed adRP and JMD. Subjects 15, 22, 36, and 43 showed both adRP and JMD. Patients with fovea centralis areflexia phenotype can be found in patients 15, 22, 36 and 43. For example, typical pigmentation can be seen on the retina of patient 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G). Similar fovea centralis areflexia phenotype can be found in patients 15, 22, 36 and 43. For example, typical pigmentation can be seen on the retina of patient 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G). Similar fovea centralis areflexia phenotype can be found in patients 15, 22, 36 and 43. For example, typical pigmentation can be seen on the retina of patient 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G). Similar fovea centralis areflexia phenotype can be found in patients 15, 22, 36 and 43. For example, typical pigmentation can be seen on the retina of patient 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G). Similar fovea centralis areflexia phenotype can be found in patients 15, 22, 36 and 43. For example, typical pigmentation can be seen on the retina of patient 13, who experienced RP onset during his childhood (Fig. 2 A, B). An exception was subject 22, who experienced RP onset at the age of 48. The other patients experienced RP onset during their childhoods. Furthermore, patient 38 exhibited features of macular degeneration in her childhood or young adulthood (Fig. 2 C-G).
subjects showed bilateral cataracts, it is difficult to diagnose the genetic factors of cataracts for RP patients over 40 years of age. RP and MD are the most common degenerative diseases of the retina. To date, about eight genes have been identified as disease-causing genes for patients with RP and/or MD. For example, mutations in ABCA4, the photoreceptor ABC transporter, are associated with Stargardt macular degeneration [5] and arRP [6–7]. Mutations in BEST1 can cause multifocal Best vitelliform MD (Best disease) [8] and adRP [9]. Mutations in FSCN2 [10–11] and PRPH2 (peripherin/RDS) [12–13] can cause adMD and adRP. Mutations in PROM1 [14–15], RP1 [16], RPE65 [17–19], and RPGR [20–21] can also cause MD and/or RP.

The PRPF31 gene codes for the splicing factor hPRP31. Mutations in PRPF31 have been repeatedly found to be associated with autosomal dominant retinitis pigmentosa (adRP). In 1994, an adRP locus on 19q13.4 (RP11) was first localized via Linkage analysis in a large British family [22]. Then, within this region, mutations in the PRPF31 gene were identified in other families and sporadic cases [23]. Mutations in PRPF31 are inherited in an autosomal dominant manner, accounting for about 5% of cases of adRP [1]. Additionally, genomic rearrangements of the PRPF31 gene account for about 2.5% of adRP cases [24–25]. Various mutations have been identified in the PRPF31 gene that are associated with adRP, including 769–770insA [26], the in-frame deletion of four amino acids 111–114 [27], splice site mutation (IVS8+1G>C) [28], A194E, A216P [29], and c. 1142 del G [30].

PRPF31 is one of the three pre-mRNA splicing factors that encode components of the spliceosome U4/U6*U5 tri-snRNP [31], which has been identified as causing adRP (the other two genes are PRPF3 and PRPF8) [26]. This complex can excise introns from RNA transcripts. The disease mechanism for RP11 is caused by mutations in the splicing factor gene PRPF31 because its’ splicing function is incomplete [32]. These spliceosomes are highly conserved in eukaryotes ranging from mammals to yeast.

The underlying mechanism via which PRPF31 causes adRP and MD is still unknown. The inheritance pattern of PRPF31 mutation is atypical of dominant inheritance [33], which suggests partial penetrance: a dominant mutation appears to “skip” generations. A significant difference in wild-type and mutant PRPF31 mRNA levels was observed between symptomatic and asymptomatic individuals; this can partially explain the incomplete penetrance phenotype of adRP caused by PRPF31 mutation [34]. However, there are probably more subtle molecular mechanisms underlying this disease [35]. In zebrafish, it was suggested that distinct mutations in PRPF31 can lead to photoreceptor degeneration via different mechanisms, such as haplo-insufficiency or dominant-negative effects [36].

The PRPF31 gene codes for 499 amino acids (55 kD). The PRPF31 protein contains three domains: NOSIC (NOSIC NUC001 domain, from 92aa to 144aa), NOP (snoRNA binding domain, from 186aa to 334aa), and Prp31C (terminal domain, from 336aa to 465aa). Previously, yeast two-hybrid analysis result had shown that the NOP domain is a genuine RNP-binding module, exhibiting RNA- and protein-binding surfaces [37]. In this study, we found a frame shift insertion mutation in the NOP domain area. This mutation causes the protein frame shift at p.307 and early termination at p.322 after coding for 15 missense amino acids. This nonsense protein suggested aberrant hPrp31-hPrp6 interaction that blocks U4/U6-U5 tri-snRNP formation, which may be the reason that the 1085 family was affected by adRP and MD.

In summary, we have, for the first time, identified a heterozygous insertion in exon9 at chr19:54629961-54629961 (UCSC:feb.2009 (GRCH37/HG190)), inserting an “A” nucleotide mutation in the PRPF31 gene, causing typical adRP and JMD. Our study provides evidence that a mutation in the
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