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### Authors

Ullah, Inayat
Kabir, Firoz
Iqbal, Muhammad
et al.



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# Pathogenic mutations in *TULP1* responsible for retinitis pigmentosa identified in consanguineous familial cases

**Inayat Ullah,[1] Firoz Kabir,[2] Muhammad Iqbal,[1] Clare Brooks S. Gottsch,[2] Muhammad Asif Naeem,[1] Muhammad Zaman Assir,[3,4] Shaheen N. Khan,[1] Javed Akram,[3,4] Sheikh Riazuddin,[1,3,4] Radha Ayyagari,[5] J. Fielding Hejtmancik,[6] S. Amer Riazuddin[2]**

**(The first two and last two authors contributed equally to the work.)**

*[1]National Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan; [2]The Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD; [3]Allama Iqbal Medical College, University of Health Sciences, Lahore, Pakistan; [4]National Centre for Genetic Diseases, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan; [5]Shiley Eye Institute, University of California, San Diego, CA; [6]Ophthalmic Genetics and Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, MD*

**Purpose:** To identify pathogenic mutations responsible for autosomal recessive retinitis pigmentosa (arRP) in consanguineous familial cases.
**Methods:** Seven large familial cases with multiple individuals diagnosed with retinitis pigmentosa were included in the study. Affected individuals in these families underwent ophthalmic examinations to document the symptoms and confirm the initial diagnosis. Blood samples were collected from all participating members, and genomic DNA was extracted. An exclusion analysis with microsatellite markers spanning the *TULP1* locus on chromosome 6p was performed, and two-point logarithm of odds (LOD) scores were calculated. All coding exons along with the exon–intron boundaries of *TULP1* were sequenced bidirectionally. We constructed a single nucleotide polymorphism (SNP) haplotype for the four familial cases harboring the K489R allele and estimated the likelihood of a founder effect.
**Results:** The ophthalmic examinations of the affected individuals in these familial cases were suggestive of RP. Exclusion analyses confirmed linkage to chromosome 6p harboring *TULP1* with positive two-point LOD scores. Subsequent Sanger sequencing identified the single base pair substitution in exon14, c.1466A>G (p.K489R), in four families. Additionally, we identified a two-base deletion in exon 4, c.286_287delGA (p.E96Gfs77*); a homozygous splice site variant in intron 14, c.1495+4A>C; and a novel missense variation in exon 15, c.1561C>T (p.P521S). All mutations segregated with the disease phenotype in the respective families and were absent in ethnically matched control chromosomes. Haplotype analysis suggested ($p<10^{-6}$) that affected individuals inherited the causal mutation from a common ancestor.
**Conclusions:** Pathogenic mutations in *TULP1* are responsible for the RP phenotype in seven familial cases with a common ancestral mutation responsible for the disease phenotype in four of the seven families.

Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous group of hereditary retinal disorders that primarily affect the ocular retina, with a prevalence of 1:4,000 [1,2]. RP is characterized by progressive degeneration of rod photoreceptors, leading to night blindness and constriction of the visual field, followed by the degeneration of cone photoreceptors, resulting in a total loss of vision [3]. The clinical manifestation of the disease includes pigmentary deposits in the retina, waxy disc pallor, and attenuation of retinal blood vessels [3]. Affected individuals often have severely abnormal or undetectable electroretinography responses, even in the early stage of the disease [3].

Correspondence to: S. Amer Riazuddin, The Wilmer Eye Institute, Johns Hopkins University School of Medicine, 600 N. Wolfe Street; Maumenee 840, Baltimore, MD 21287; Phone: (410) 955-3656; FAX: (410) 955-3656; email: riazuddin@jhmi.edu

RP is a genetically heterogeneous disorder that manifests as an autosomal dominant, autosomal recessive, or X-linked trait. To date, a total of 73 genes have been implicated in the pathogenesis of RP. Of these, 27 genes have been associated with autosomal dominant RP (adRP) [4-30], while mutations in 50 genes have been identified in patients with autosomal recessive RP (arRP) [31-77]. Mutations in *RHO* (Gene ID: 6010; OMIM: 180380), *RP1* (Gene ID: 6101; OMIM: 603937), *NRL* (Gene ID: 4901; OMIM: 162080), *RPE65* (Gene ID: 6121; OMIM: 180069), *BEST1* (Gene ID: 7439; OMIM: 607854), *NR2E3* (Gene ID: 10,002; OMIM: 604485), and *IMPDH1* (Gene ID: 3614; OMIM: 146690) have been identified in familial cases of adRP and arRP. Likewise, causal mutations in *OFD1* (Gene ID: 8481; OMIM: 300170), *RP2* (Gene ID: 6102; OMIM: 300757), and *RPGR* (Gene ID: 6103; OMIM: 312610) have been identified in RP cases with an X-linked inheritance pattern [78-80].

The *tubby-like protein 1* (*TULP1*) gene consists of 15 coding exons spanning a 15 kb region and encodes for a 542 amino acid protein that has been associated with the transport of rhodopsin from its site of synthesis in the inner segments through the connecting cilium to the outer segments [81]. North and colleagues previously reported that *TULP1* is expressed in many tissues, specifically in the rod and cone photoreceptor cells, and is involved in the transport of rhodopsin [82]. *TULP1* has been associated with retinal degeneration, and pathogenic mutations in *TULP1* have been identified in patients with arRP, rod-cone dystrophy, and Leber congenital amaurosis (LCA).

We previously reported five familial cases of arRP harboring mutations in *TULP1* [83]. Since Iqbal et al. published their study, we have ascertained more than 200 familial cases of arRP. To investigate the genetic load of *TULP1* in our familial cohort, we performed an exclusion linkage analysis that identified seven additional intermarried familial cases with multiple consanguineous marriages, diagnosed with early-onset RP. Clinical records available to us suggest an early, probably congenital onset, while exclusion analysis localized the retinal phenotype in all seven families to chromosome 6p harboring *TULP1*. Sanger sequencing of *TULP1* identified causal mutations that segregated with the disease phenotype in the respective families and were absent in ethnically matched controls and genome-variant databases.

## METHODS

*Clinical ascertainment:* A total of more than 350 consanguineous Pakistani families with non-syndromic retinal dystrophies were recruited to identify new disease loci responsible for inherited visual diseases. The Institutional Review Boards (IRBs) of the National Centre of Excellence in Molecular Biology (Lahore, Pakistan), the National Eye Institute (Bethesda, MD), and Johns Hopkins University (Baltimore, MD) approved the study. All participating family members

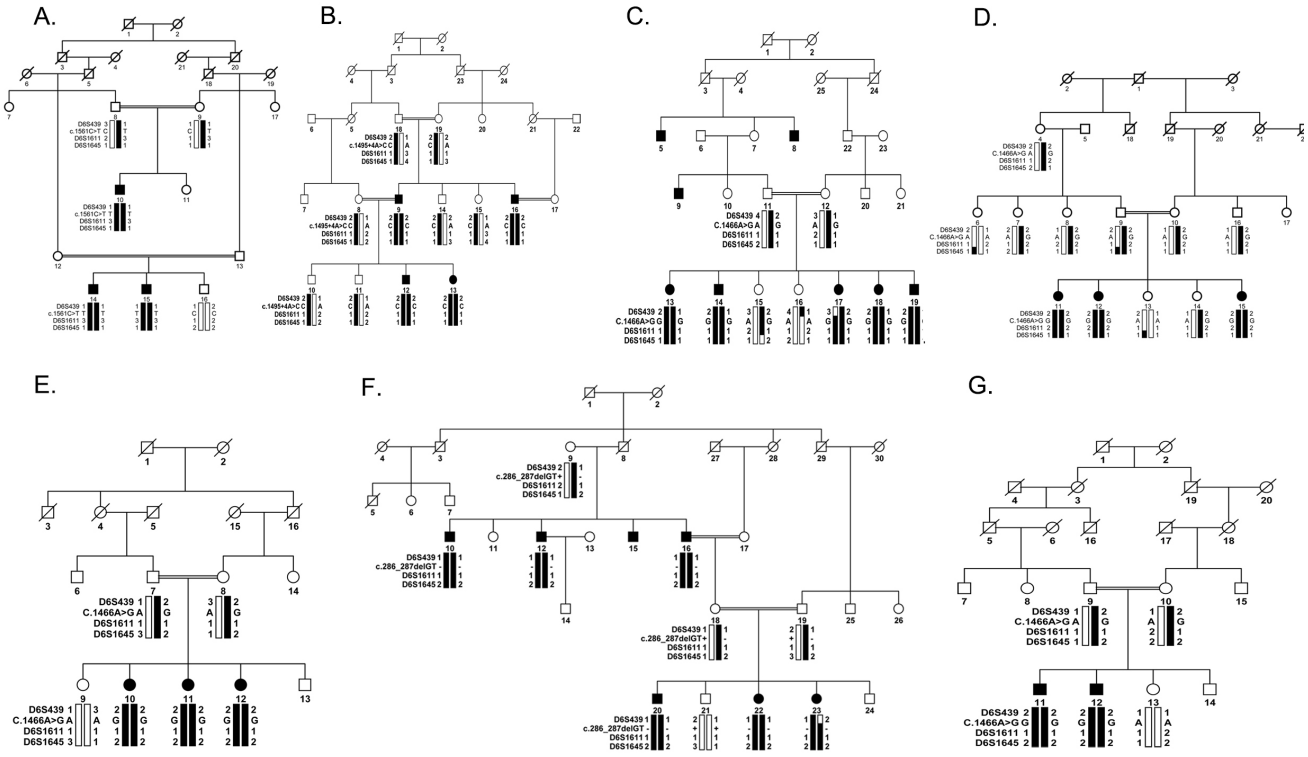


Figure 1. Pedigree drawings with haplotype formed from alleles of chromosome 6p microsatellite markers. **A**: PKRP259. **B**: PKRP268. **C**: PKRP301. **D**: PKRP309. **E**: PKRP356. **F**: PKRP364. **G**: PKRP367. The alleles forming the risk haplotype are shaded black, and the alleles that do not cosegregate with retinitis pigmentosa (RP) are shown in white. Squares = males; circles = females; filled symbols = affected individuals; double line between individuals = consanguineous marriage; diagonal line through a symbol = deceased family member.

Table 1. Clinical characteristics of the patients screened for *TULP1* mutations.

| Family | ID | C-Age (Yr.) | D-age (Yr.) | First symptoms | Night blindness | Fundus examination | Electroretinography | | Visual acuity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | OD | OS | OD | OS |
| PKRP259 | 10 | 28 | 6 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/36 | 6/40 |
| PKRP259 | 15 | 22 | 7 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/24 | 6/24 |
| PKRP268 | 12 | 17 | 7 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/20 | 6/20 |
| PKRP268 | 13 | 14 | 6 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/20 | 6/20 |
| PKRP301 | 14 | 20 | 5 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/18 | 6/20 |
| PKRP301 | 17 | 14 | 5 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/20 | 6/24 |
| PKRP309 | 11 | 34 | 6 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/30 | 6/28 |
| PKRP309 | 15 | 25 | 7 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/25 | 6/25 |
| PKRP356 | 10 | 10 | 5 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/12 | 6/12 |
| PKRP356 | 12 | 8 | 5 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/20 | 6/20 |
| PKRP364 | 10 | 58 | 7 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/50 | 6/50 |
| PKRP364 | 20 | 21 | 8 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/24 | 6/24 |
| PKRP367 | 11 | 31 | 6 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/24 | 6/28 |
| PKRP367 | 12 | 20 | 7 | Night blindness | progressive | MD, Art. Atten, Pig.dep, PD | NAB, NF | NAB, NF | 6/20 | 6/20 |

MD: macular degeneration; Art. Atten: artery attenuation; Pig.dep: pigment deposit; PD: Pale optic disc; NAB: no ‘a’ or ‘b’ wave response; NF: no flicker response; C-Age: current age; D-Age: age at first diagnosis of the retinal dystrophy.

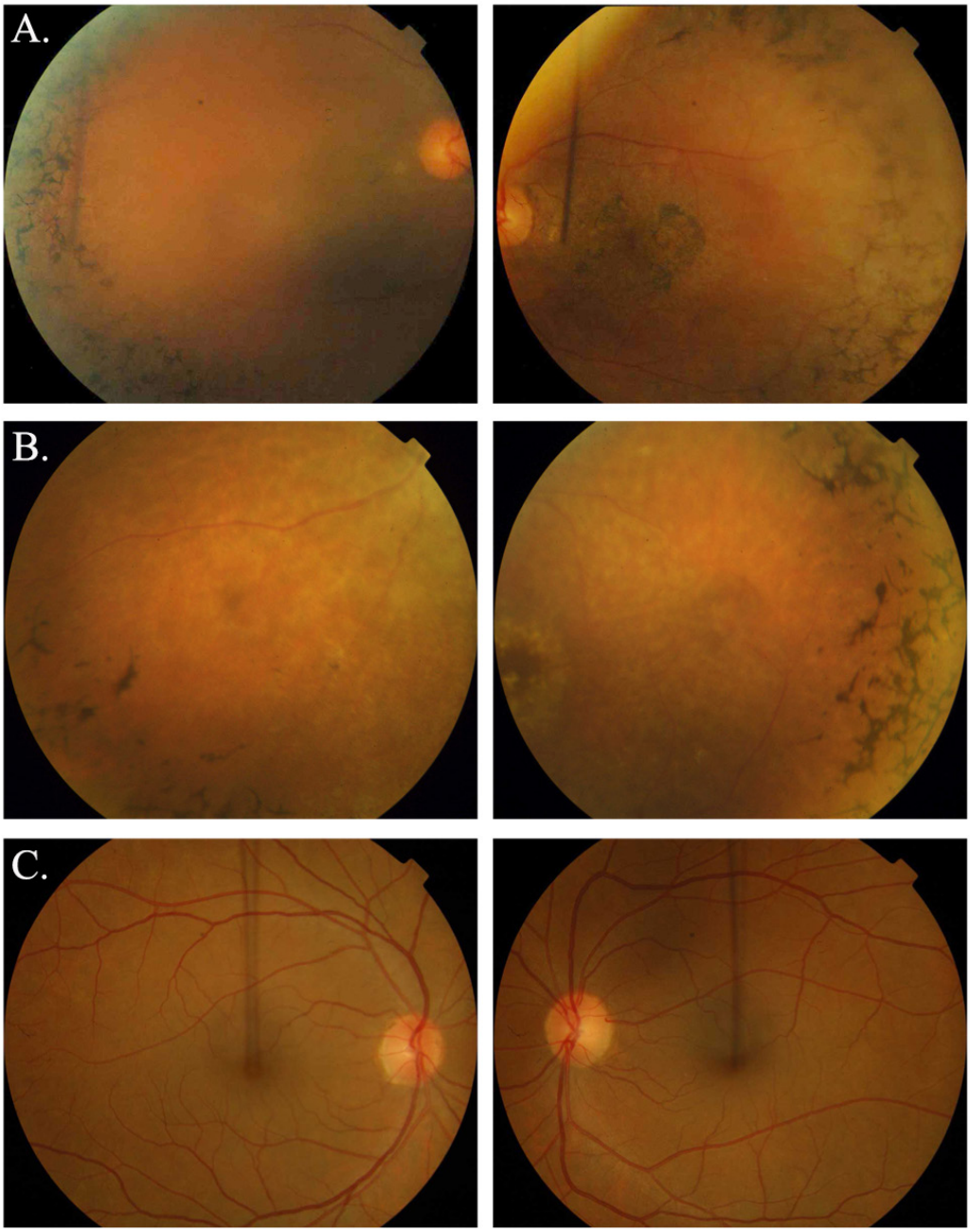


Figure 2. Fundus photographs of affected individuals illustrating symptoms of retinitis pigmentosa. **A**: OD and OS of individual 10 (affected: 30 years) of family PKRP259. **B**: OD and OS of individual 11 (affected: 18 years) of family PKRP309. **C**: OD and OS of individual 8 (unaffected: 52 years) of family PKRP259. Fundus photographs of affected individuals show bone spicule-like pigmentation in the mid-periphery of the retina, attenuated retinal arterioles, severe maculopathy, and disc pallor. OD = oculus dexter; OS = oculus sinister.

provided informed written consent that was endorsed by the respective IRBs and is consistent with the tenets of the Declaration of Helsinki.

A detailed clinical and medical history was obtained by interviewing the family members. Funduscopy was performed at the Layton Rehmatulla Benevolent Trust (LRBT) Hospital (Lahore, Pakistan). Electroretinography (ERG) measurements were recorded by using equipment manufactured by LKC (Gaithersburg, MD). Dark-adapted rod responses were determined through incident flash attenuated by −25 dB, whereas rod–cone responses were measured at 0 dB. The 30 Hz flicker responses were recorded at 0 dB to a background illumination of 17 to 34 cd/m$^2$. All participating members voluntarily provided a sample of approximately 10 ml of blood that was stored in 50 ml Sterilin® falcon tubes containing 400 µl of 0.5 M EDTA. The blood samples were stored at −20 °C for long-term storage.

*Genomic DNA extraction:* Genomic DNA was extracted from white blood cells using a non-organic modified procedure as described previously [84]. The concentration of the extracted genomic DNA was estimated with a SmartSpec Plus Spectrophotometer (Bio-Rad, Hercules, CA).

*Exclusion and linkage analysis:* PCR was performed in a 5 µl mixture containing 40 ng of genomic DNA, 0.5 µl of 10 µM fluorescent-labeled primer pairs, 0.5 µl of 10X PCR Buffer (100 mM Tris HCl (pH 8.4), 400 mM NaCl, 15 mM $MgCl_2$, 2.5 mM spermidine), 2 mM dNTP mix, and 0.2 U Taq DNA Polymerase (New England BioLabs Inc., Ipswich, MA). Initial denaturation was performed for 5 min at 95 °C, followed by ten cycles of 15 s at 94 °C, 15 s at 55 °C, and 30 s at 72 °C and then 20 cycles of 15 s at 89 °C, 15 s at 55 °C, and

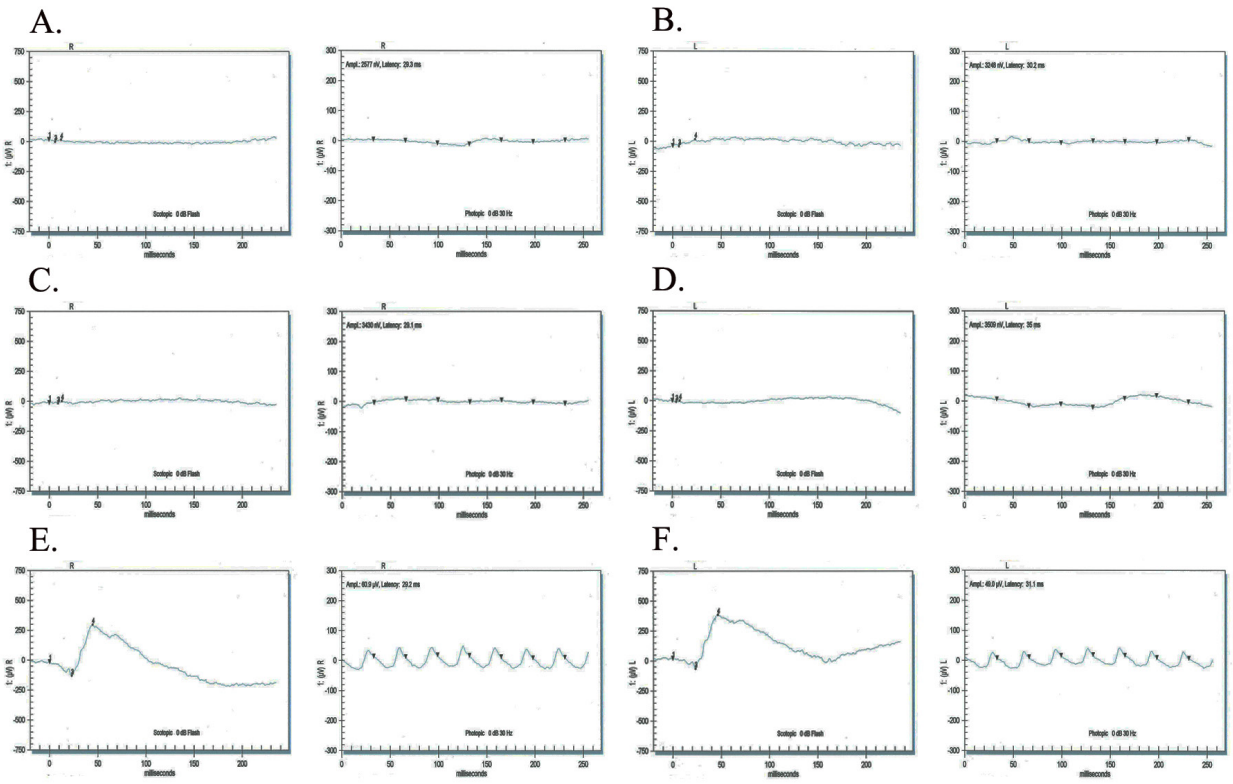


Figure 3. Electroretinography responses of PKRP259 family members. In the stimulus conditions, scotopic 0 dB bright flashes elicit rod responses (left column of each pair), and a photopic 0 dB, 30 Hz flicker elicits cone responses (right column of each pair). Responses are of **A**) OD and **B**) OS of individual 10 (affected: 30 years); **C**) OD and **D**) OS of individual 14 (affected: 25 years); and **E**) OD and **F**) OS of individual 8 (unaffected: 52 years). The affected individuals exhibit undetectable electroretinography responses whereas the unaffected individual exhibits normal a- and b-waves suggestive of normal rod and cone function. OD = oculus dexter; OS = oculus sinister.

30 s at 72 °C. The final extension was performed for 10 min at 72 °C. PCR products were mixed with a loading cocktail containing HD-400 size standards (Applied Biosystems, Foster City, CA) and resolved in an ABI PRISM 3100 Genetic Analyzer. Genotypes were assigned using Gene Mapper software from Applied Biosystems.

Linkage analysis was performed with alleles obtained through exclusion analysis using the FASTLINK version of MLINK from the LINKAGE Program Package [85,86]. Maximum LOD scores were calculated using ILINK from the LINKAGE Program Package. Autosomal recessive RP was investigated as a fully penetrant disorder with an affected allele frequency of 0.001. The marker order and distances between the markers were obtained from the National Center for Biotechnology Information chromosome 6 sequence maps.

*Mutation screening:* Individual exons of *TULP1* were amplified with PCR using primer pairs designed by the primer3 program (Appendix 1). PCR reactions were completed in 10 µl volumes containing 20 ng of genomic DNA, 1 µl of the forward and reverse primers at 10 µM, 1 µl of 10X PCR Buffer (100 mM Tris HCl (pH 8.4), 400 mM NaCl, 15 mM $MgCl_2$, 2.5 mM spermidine), 2 mM dNTP mix, 500 mM betaine, and 0.2 U Taq DNA Polymerase. PCR amplification

Table 2. Two-point LOD scores of chromosome 6p markers for families A) PKRP259, B) PKRP268, C) PKRP301, D) PKRP309, E) PKRP356, F) PKRP364, and G) PKRP367.

| Markers | cM | Mb | 0.00 | 0.01 | 0.05 | 0.09 | 0.10 | 0.20 | 0.30 | $Z_{max}$ | $\theta_{max}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **A** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | 2.21 | 2.16 | 1.95 | 1.74 | 1.68 | 1.15 | 0.65 | 2.21 | 0.00 |
| D6S1611 | 47.71 | 35.40 | 2.79 | 2.73 | 2.50 | 2.26 | 2.20 | 1.57 | 0.93 | 2.79 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 2.02 | 1.97 | 1.77 | 1.57 | 1.51 | 1.00 | 0.51 | 2.02 | 0.00 |
| **B** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | 2.30 | 2.26 | 2.06 | 1.86 | 1.80 | 1.27 | 0.72 | 2.30 | 0.00 |
| D6S1611 | 47.71 | 35.40 | 2.48 | 2.43 | 2.22 | 2.00 | 1.94 | 1.39 | 0.85 | 2.48 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 3.33 | 3.26 | 2.99 | 2.72 | 2.65 | 1.94 | 1.22 | 3.33 | 0.00 |
| **C** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | -∞ | −5.70 | −3.82 | −2.96 | −2.40 | −2.00 | −1.83 | −2.00 | 0.20 |
| D6S1611 | 47.71 | 35.40 | 1.14 | 1.12 | 1.07 | 1.02 | 0.97 | 0.93 | 0.90 | 1.14 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 1.44 | 1.40 | 1.33 | 1.25 | 1.18 | 1.11 | 1.07 | 1.44 | 0.00 |
| **D** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | 1.55 | 1.52 | 1.46 | 1.39 | 1.33 | 1.27 | 1.23 | 1.55 | 0.00 |
| D6S1611 | 47.71 | 35.40 | 1.58 | 1.55 | 1.48 | 1.42 | 1.35 | 1.28 | 1.25 | 1.58 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 0.66 | 0.64 | 0.61 | 0.58 | 0.55 | 0.52 | 0.50 | 0.66 | 0.00 |
| **E** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | 2.19 | 2.15 | 2.06 | 1.98 | 1.89 | 1.80 | 1.76 | 2.19 | 0.00 |
| D6S1611 | 47.71 | 35.40 | 0.49 | 0.47 | 0.44 | 0.41 | 0.38 | 0.35 | 0.33 | 0.49 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 2.19 | 2.15 | 2.06 | 1.98 | 1.89 | 1.80 | 1.76 | 2.19 | 0.00 |
| **F** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | -∞ | −0.81 | 0.01 | 0.33 | 0.50 | 0.59 | 0.62 | 0.62 | 0.30 |
| D6S1611 | 47.71 | 35.40 | 2.03 | 1.98 | 1.89 | 1.79 | 1.69 | 1.59 | 1.54 | 2.03 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 3.93 | 3.86 | 3.71 | 3.56 | 3.41 | 3.25 | 3.17 | 3.93 | 0.00 |
| **G** | | | | | | | | | | | |
| D6S439 | 48.26 | 35.18 | 0.73 | 0.71 | 0.64 | 0.45 | 0.10 | 0.20 | 0.30 | 0.73 | 0.00 |
| D6S1611 | 47.71 | 35.40 | 0.43 | 0.42 | 0.37 | 0.46 | 0.55 | 0.37 | 0.19 | 0.43 | 0.00 |
| D6S1645 | 48.26 | 35.61 | 0.43 | 0.42 | 0.37 | 0.46 | 0.32 | 0.20 | 0.10 | 0.43 | 0.00 |

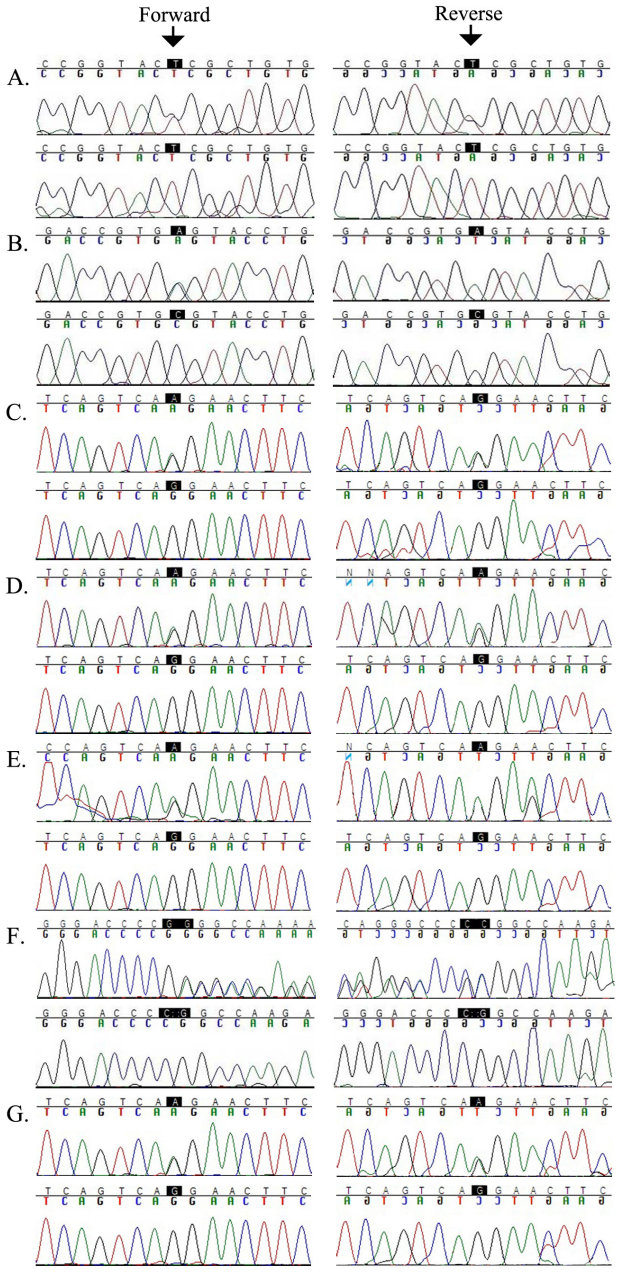


Figure 4. Sequence chromatograms of *TULP1* variations identified in this study. **A**: Unaffected individual 8 is a heterozygous carrier, and affected individual 10 is homozygous for the single base pair substitution c.1561C>T in family PKRP259. **B**: Unaffected individual 19 is a heterozygous carrier, and affected individual 12 is homozygous for the splice region variant c.1495+4A>C in family PKRP268. **C**: Unaffected individual 12 is a heterozygous carrier, and affected individual 17 is homozygous for the single base pair substitution c.1466A>G in family PKRP301. **D**: Unaffected individual 7 is a heterozygous carrier, and affected individual 15 is homozygous for the single base pair substitution c.1466A>G in family PKRP309. **E**: Unaffected individual 8 is a heterozygous carrier, and affected individual 10 is homozygous for the single base pair substitution c.1466A>G in family PKRP356. **F**: Unaffected individual 18 is a heterozygous carrier, and affected individual 10 is homozygous for the two-base deletion c.286_287delGA in family PKRP364. **G**: Unaffected individual 9 is a heterozygous carrier, and affected individual 12 is homozygous for the single base pair substitution c.1466A>G in family PKRP367.

| | $C_{523}$ | $L_{522}$ | $P_{521}$ | $Y_{520}$ | $R_{519}$ | $T_{1495+6}$ | $G_{1495+5}$ | $A_{1495+4}$ | $G_{1495+3}$ | $T_{1495+2}$ | $G_{1495+1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Human | C | L | P | Y | R | T | G | A | G | T | G |
| Chimp | C | L | P | Y | R | T | G | A | G | T | G |
| Gorrila | C | L | P | Y | R | T | G | A | G | T | G |
| Orangutan | C | L | P | Y | R | T | G | A | G | T | G |
| Gibbon | C | L | P | Y | R | T | G | A | G | T | G |
| Rhesus | C | L | P | Y | R | T | G | A | G | T | G |
| Crab-eating macaque | C | L | P | Y | R | T | G | A | G | T | G |
| Baboon | C | L | P | Y | R | T | G | A | G | T | G |
| Green monkey | C | L | P | Y | R | T | G | A | G | T | G |
| Marmoset | C | L | P | Y | R | T | G | A | G | T | G |
| Squirrel monkey | C | L | P | Y | R | T | G | A | G | T | G |
| Bushbaby | C | L | P | Y | R | T | G | A | G | T | G |
| Chinese tree shrew | C | L | P | Y | R | T | G | A | A | T | G |
| Squirrel | C | L | P | Y | R | T | G | A | A | T | G |
| Lesser Egyptian jerboa | C | L | P | Y | R | T | G | A | G | T | G |
| Prairie vole | C | L | P | Y | R | T | G | A | G | T | G |
| Chinese hamster | C | L | P | Y | R | T | G | A | G | T | G |
| Golden hamster | C | L | P | Y | R | T | G | A | G | T | G |
| Mouse | C | L | P | Y | R | T | G | A | G | T | G |
| Rat | C | L | P | Y | R | T | G | A | G | T | G |
| Naked mole-rat | C | L | P | Y | R | T | G | A | G | T | G |
| Guinea pig | C | L | P | Y | R | T | G | A | G | T | G |
| Chinchilla | C | L | P | Y | R | T | G | A | G | T | G |
| Brush tailed rat | C | L | P | Y | Q | T | G | A | G | T | G |
| Rabbit | C | L | P | Y | R | T | G | A | A | T | G |
| Pika | C | L | P | Y | R | C | G | A | G | T | G |
| Pig | C | L | P | Y | R | T | G | A | G | T | G |
| Alpaca | C | L | P | Y | R | T | G | A | G | T | G |
| Bactrian camel | C | L | P | Y | R | T | G | A | G | T | G |
| Dolphin | C | L | P | Y | R | T | G | A | G | T | G |
| Killer whale | C | L | P | Y | R | T | G | A | G | T | G |
| Tibetan antelope | C | L | P | Y | R | T | G | A | G | T | G |
| Cow | C | L | P | Y | R | T | G | A | G | T | G |
| Sheep | C | L | P | Y | R | T | G | A | G | T | G |
| Domestic goat | C | L | P | Y | R | T | G | A | G | T | G |
| Horse | C | L | P | Y | R | T | G | A | G | T | G |
| White rhinoceros | C | L | P | Y | R | T | G | A | G | T | G |
| Cat | C | L | P | Y | R | T | G | A | G | T | G |
| Dog | C | L | P | Y | R | T | G | A | G | T | G |
| Ferret | C | L | P | Y | R | T | G | A | G | T | G |
| Panda | C | L | P | Y | R | T | G | A | G | T | G |
| Pacific walrus | C | L | P | Y | R | T | G | A | G | T | G |
| Weddell seal | C | L | P | Y | R | T | G | A | G | T | G |
| Black flying-fox | C | L | P | Y | R | T | G | A | G | T | G |
| Megabat | C | L | P | Y | R | T | G | A | G | T | G |
| David's myotis (bat) | C | L | P | Y | R | T | G | A | G | T | G |
| Microbat | ~ | ~ | ~ | ~ | ~ | T | G | A | G | T | G |
| Big brown bat | C | L | P | Y | R | T | G | A | G | T | G |
| Hedgehog | C | L | P | Y | R | T | G | A | G | T | G |
| Shrew | C | L | P | Y | R | T | G | A | G | T | G |
| Star-nosed mole | C | L | P | Y | R | T | G | A | G | T | G |
| Elephant | C | L | P | Y | R | T | G | A | G | T | G |
| Cape elephant shrew | C | L | P | Y | R | T | G | A | G | T | G |
| Manatee | C | L | P | Y | R | T | G | A | G | T | G |
| Cape golden mole | C | L | P | Y | R | T | G | A | G | T | G |
| Tenrec | C | L | P | Y | R | T | G | A | G | T | G |
| Aardvark | C | L | P | Y | R | T | G | A | G | T | G |

Figure 5. Sequence conservation of amino acid Pro521 and nucleotide 1495+4A in TULP1 orthologs. Primates are green, placental mammals are blue, and vertebrates are purple. The arrow points to amino acid residue Pro521 and nucleotide 1495+4A, which were mutated in individuals with retinitis pigmentosa.

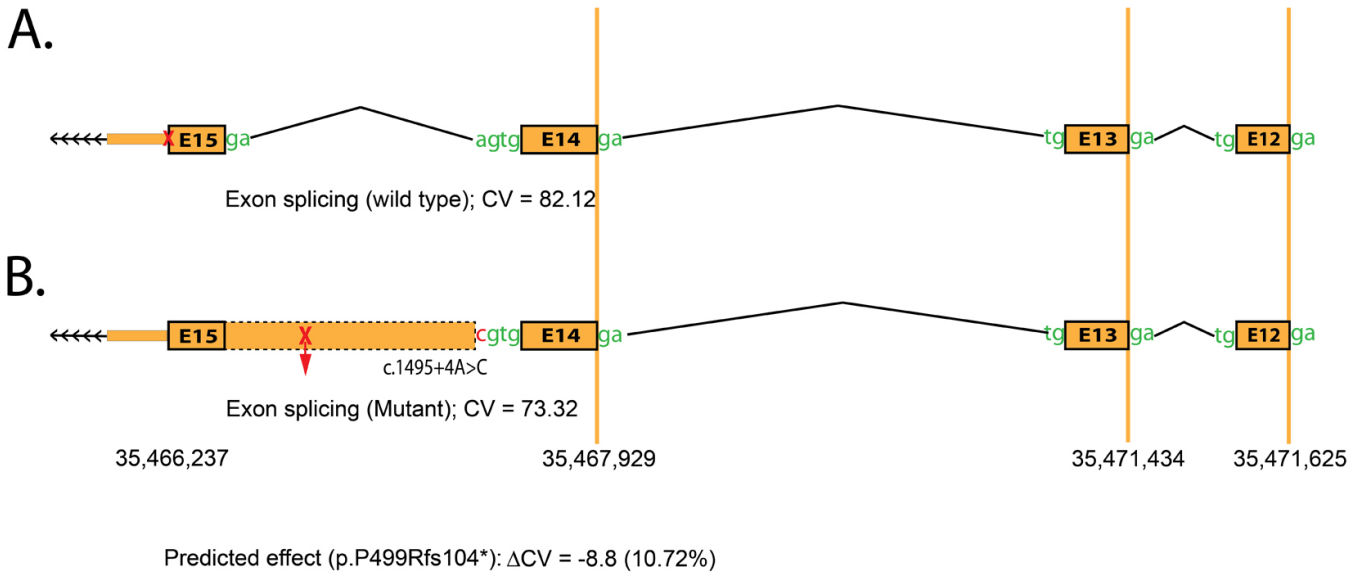


Figure 6. *In silico* analysis of the splice donor site mutation in *TULP1*. The HSF3 algorithm predicted a consensus value (CV) of **A**) 82.12 for the wild-type (c.1495+4A) and **B**) 73.32 (c.1495+4C) for the mutant splice donor site. The CV deviation of −10.72 suggests that the loss of the wild-type splice site will result in the retention of intron 14 of *TULP1*, resulting in a frame shift likely to produce aberrant TULP1 (p.P499Rfs104*).

consisted of a denaturation step at 95 °C for 5 min followed by a two-step touchdown procedure. The first step of ten cycles consisted of denaturation at 95 °C for 30 s, followed by a primer set-specific annealing for 30 s (annealing temperature decreased by 1 °C per cycle) and elongation at 72 °C for 45 s. The second step of 30 cycles consisted of denaturation at 95 °C for 30 s, followed by annealing (10 °C below the annealing temperature used in the first step) for 30 s and elongation at 72 °C for 45 s, followed by a final elongation at 72 °C for 5 min.

The PCR primers for each amplicon were used for bidirectional sequencing using the BigDye Terminator Ready Reaction mix according to the manufacturer's instructions. The sequencing products were resolved on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems), and results were analyzed with Applied Biosystems SeqScape software.

*In silico analysis:* The degree of evolutionary conservation of c.1495+4A>C in other *TULP1* orthologs was examined using the UCSC Genome browser. The effect of the c.1495+4A>C mutation on *TULP1* mRNA splicing was predicted with an online bioinformatics tool, Human Splicing Finder 3.0 (HSF3). The possible impact of an amino acid change in the structure of TULP1 was examined with the SIFT and PolyPhen-2 tools available online.

*Estimating the likelihood of a common founder effect:* A total of five single nucleotide polymorphisms (SNPs) within 11 kb

Table 3. Single nucleotide polymorphism (SNP) haplotypes of affected individuals in PKRP301, PKRP309, PKRP356, and PKRP367 harboring the c.1466A>G (p.K489R) mutation in *TULP1*.

| Family | Individual | c.1466A>G | rs12665445 | rs7770128 | rs12215920 | rs34126023 | rs7764472 |
|---|---|---|---|---|---|---|---|
| | | Chr6: 35500039 | Chr6: 35500262 | Chr6: 35505901 | Chr6: 35506296 | Chr6: 35509796 | Chr6: 35511797 |
| **PKRP301** | 14 | G | C | T | G | T/C | C |
| **PKRP309** | 15 | G | C | T | G | T/C | C |
| **PKRP356** | 10 | G | C | T | G | T/C | C |
| **PKRP367** | 12 | G | C | T | G | T/C | C |

Table 4. List of mutations reported in *TULP1*-associated retinal dystrophies.

| Exon/ Intron | Nucleotide change | Amino acid change | Phenotype | Reference |
|---|---|---|---|---|
| Exon 1 | c.3G>A | p.M1I | arRP | 87 |
| Intron 2 | c.99+1G>A | Aberrant splicing | LCA, arRP | 88, 89 |
| Exon 4 | c.280G>T | p.D94Y | LCA | 90 |
| Intron 4 | c.350–2delAGA, (IVS4–2delAGA) | Aberrant splicing | arRP | 91 |
| Exon 5 | c.394_417del | p.E120_D127del | arRP | 92 |
| Exon 5 | c.539G>A | p.R180H | LCA | 93 |
| Exon 6 | c.627delC | p.S210QfsX27 | LCA | 94 |
| Exon 6 | c.629C>G | p.S210* | RP | 95 |
| Intron 7 | c.718+2T>C | Aberrant splicing | JRP, LCA | 96 |
| Exon 7 | c.725_728delCCAA | p.P242Qfs×16 | LCA | 97 |
| Exon 10 | c.901C>T | p.Q301* | LCA, RCD | 98, 99 |
| Exon 10 | c.937delC | p.Q301fs9* | arRP | 91 |
| Exon 10 | c.932G>A | p.R311Q | arRP | 100 |
| Exon 10 | c.956G>A | p.G319D | RP | 101 |
| Exon 10 | c.961T>G | p.Y321D | LCA | 97 |
| Intron 10 | c.999+5G>C | Aberrant splicing | JRP, LCA | 96 |
| Exon 11 | c.1025G>A | p.R342Q | arRP | 100 |
| Exon 11 | c.1047T>G | p.N349K | arRP | 102 |
| Exon 11 | c.1064A>T | p.D355V | LCA | 97 |
| Exon 11 | c.1087G>A | p.G363R | RCD | 103 |
| Exon 11 | c.1081C>T | p.R361* | LCA | 104 |
| Exon 11 | c.1102G>T | p.G368W | LCA | 89 |
| Intron 11 | c.1112+2T>C (IVS11 ds T-C +2) | Aberrant splicing | arRP | 105 |
| Intron 11 | c.1113–2A>C (IVS11 as A-C −2) | Aberrant splicing | LCA | 97 |
| Exon 12 | c.1138A>G | p.T380A | LCA, arRP | 83, 106, 107 |
| Exon 12 | c.1145T>C | p.F382S | arRP | 108 |
| Exon 12 | c.1198C>T | p.R400W | arRP, LCA, RD | 89, 109, 110 |
| Exon 12 | c.1199G>A | p.A400Q | arRP | 111 |
| Exon 12 | c.1204G>T | p.E402* | LCA | 89 |
| Intron 12 | c.1224+4A>G, (IVS12+4A>G) | Aberrant splicing | arRP | 92 |
| Exon 13 | c.1246C>T | p.R416C | ArRP | 87 |
| Exon 13 | c.1258C>A | p.R420S | RCD | 112 |
| Exon 13 | c.1259G>C | p.R420P | arRP | 88 |

| Exon/ Intron | Nucleotide change | Amino acid change | Phenotype | Reference |
|---|---|---|---|---|
| Exon 13 | c.1318C>T | p.R440* | LCA | 94 |
| Exon 14 | c.1349G>A | p.W450* | LCA | 90 |
| Exon 14 | c.1376T>A | p.I459K | arRP | 37, 88 |
| Exon 14 | c.1376T>C | p.I459T | arRP | 105 |
| Exon 14 | c.1376_1377delTA | p.I459Rfs×12 | LCA | 97 |
| Exon 14 | c.1381C>G | p.L461V | JRP, LCA | 96 |
| Exon 14 | c.1444C>T | p.R482W | arRP | 81, 109 |
| Exon 14 | c.1445G>A | p.A482Q | arRP | 107 |
| Exon 14 | c.1466A>G | p.K489R | arRP | 83, 92, 113 |
| Exon 14 | c.1472T>C | p.F491L | arRP | 88 |
| Intron 14 | c.1495+1G>A, (IVS14+1G>A) | Aberrant splicing | arRP | 37 |
| Intron 14 | c.1495+2_1495+3insT | Aberrant splicing | arRP | 114 |
| Intron 14 | c.1496−6C>A, (IVS14−6C>A) | Aberrant splicing | arRP | 88, 92 |
| Exon 15 | c.1511_1521delTGCAGTTCGGC | p.L504fs140* | arRP | 81 |
| Exon 15 | c.1518C>A | p.F506L | LCA | 94 |
| Exon 15 | c.1582_1587dupTTCGCC | p.F528_A529dup | LCA/arRP | 115 |
| Exon 15 | c.1604T>C | p.F535S | LCA | 116 |

arRP: autosomal recessive RP; RD: Retinal degeneration; LCA: Leber congenital amaurosis; JRP: Juvenile onset RP; RCD: Rod-Cone Dystrophy.

of *TULP1* were selected, and one affected individual from each family was genotyped to construct the causal haplotype. SNP genotypes of 96 individuals of Pakistani descent were obtained from the 1000 Genomes database and used to construct ethnically matched control haplotypes. The haplotype frequencies were estimated to calculate the likelihood of a common founder effect.

## RESULTS

We ascertained a large cohort of highly intermarried familial cases of retinal dystrophies to investigate the genetic basis of arRP. We previously reported five familial cases of arRP harboring pathogenic mutations in *TULP1* [83]. Since Iqbal and colleagues [83] published their study, we have ascertained more than 200 additional familial cases of arRP, and therefore, we reexamined our expanded cohort for mutations in *TULP1* with closely spaced fluorescently labeled short tandem repeat (STR) markers spanning the *TULP1* locus. These analyses identified seven additional intermarried families (PKRP259, PKRP268, PKRP301, PKRP309, PKRP356, PKRP364, and PKRP367) linked to *TULP1* (Figure 1).

Affected individuals in these families fulfilled the diagnostic criteria of RP (Table 1). Fundus photographs of affected individuals revealed typical symptoms of RP, including attenuated retinal arteries, a waxy, pale optic disc, and bone spicule–like pigment deposits in the lateral and midperiphery of the retina (Figure 2). Likewise, scotopic ERG recordings measured at −25 dB and photopic responses at 0 dB (30 Hz flicker) were undetectable in affected individuals, suggestive of compromised rod and cone photoreceptor cells, while unaffected individuals exhibited rod and cone responses in the normal range (Figure 3).

All seven families yielded positive two-point LOD scores for chromosome 6p markers flanking *TULP1* (Table 2). We sequenced all coding exons and the exon–intron boundaries of *TULP1*, which identified four different causal mutations. They included a novel missense variation in exon 15, c.1561C>T (p.P521S), in PKRP259 (Figure 4A); a homozygous splice site variant in intron 14, c.1495+4A>C, in PKRP268 that affects the conserved splice donor site (Figure 4B); a single base pair substitution in exon 14, c.1466A>G (p.K489R), in four families, PKRP301 (Figure 4C), PKRP309 (Figure 4D), PKRP356 (Figure 4E), and PKRP367 (Figure 4G); and a two-base deletion in exon 4, c.286_287delGA (p.E96Gfs77*), in PKRP364 (Figure 4F). These variants segregated in their respective families: Affected individuals were homozygous whereas unaffected individuals were heterozygous carriers or homozygous for the wild-type allele. These mutations were absent in ethnically matched control chromosomes and were not present in the 1000 Genomes database.

We examined the evolutionary conservation of amino acid Pro521 and nucleotide c.1495+4A and found that Pro521 and c.1495+4A are completely conserved in *TULP1* orthologs (Figure 5). We examined the possible impact of the Pro521Ser substitution on the TULP1 protein using the PolyPhen-2 algorithm, which suggested that the serine substitution at position 521 would probably be damaging. Subsequently, we evaluated the effect of the c.1495+4A>C variation on *TULP1* mRNA splicing using Human Splice Finder 3 (HSF3). HSF3 generated consensus values of 82.12 and 73.32 for the wild-type (c.1495+4A) and mutant (c.1495+4C) nucleotides, respectively (Figure 6A,B). The predicted consensus value deviation of −10.72 for c.1495+4A>C suggests that the wild-type splice donor site will be broken. Loss of the wild-type splice site will result in the retention of intron 14 of *TULP1* (Figure 6B), resulting in a frame shift and is likely to produce aberrant TULP1 (p.P499Rfs104*).

All four families (PKRP301, PKRP309, PKRP356, and PKRP367) harboring the K489R allele were recruited from the Punjab province of Pakistan; they reside in different cities with no known relationship between them. We previously reported four families (PKRP084, PKRP111, PKRP122, and PKRP171) harboring the same missense variation, and SNP analysis suggested a common ancestor who transmitted the causal allele [83]. The presence of a common causal mutation in eight familial cases of our cohort prompted us to investigate the ancestral relationships among the cases. We used single nucleotide polymorphisms in the immediate neighborhood of the causal mutation, which identified a haplotype (CTGT/CC) common to all four families harboring the K489R allele (Table 3) suggestive of a common founder effect. To confirm the effect, we retrieved the genotype information of ethnically matched controls from the 1000 Genomes database and estimated the respective population haplotype frequencies (four of the five SNPs, including rs12665445, rs7770128, rs12215920, and rs7764472, were to construct the haplotype). The CTGC haplotype had an allele frequency of 0.04 in the Punjabi population of Pakistani decent, which suggested a high probability ($p>2.56\times10^{-6}$) that affected individuals in these four families inherited the causal mutation from a common ancestor. Interestingly, these odds increased significantly ($p>6.5\times10^{-12}$) when PKRP084, PKRP111, PKRP122, and PKRP171 (harboring the K489R allele reported by Iqbal et al. [83]) were included in the analysis.

## DISCUSSION

Here, we report seven consanguineous families recruited from the Punjab province of Pakistan with multiple members manifesting cardinal symptoms of RP. Exclusion analysis with closely spaced STR markers localized the linkage interval in all seven families to chromosome 6p21.3 harboring *TULP1*, while bidirectional Sanger sequencing of *TULP1* identified a novel missense variation, a splice site variant, a previously reported single base pair substitution, and a two-base deletion. All these variants segregate with the disease phenotype in the respective families. These variations were absent in 190 ethnically matched control chromosomes, and the absence of the variants in the 1000 Genomes database, the NHLBI Exome Variant Server, and the dbSNP database strongly suggests that these variations are responsible for the retinal phenotype of the patients reported in this study.

As shown in Table 4, a total of 50 causal mutations have been reported in *TULP1*, and mutations in *TULP1* account for 1–2% of arRP cases in different ethnic populations worldwide [37,81,83,87-116]. Previously, Gu and colleagues screened a large cohort of patients of German origin with arRP and identified the K489R pathogenic allele in *TULP1* [92]. More recently, Maria and colleagues identified the K489R allele in a family of Pakistani descent [113]. We found the same residue, p.K489R, in eight families; therefore, this allele is by far the most abundant RP-associated allele of *TULP1* found in the Pakistani population. In our large cohort of more than 350 familial cases of arRP, we identified 12 families harboring causal mutations in *TULP1*; however, as eight of these families harbor a common ancestral mutation, we estimate that *TULP1* contributes nearly 1% of the total genetic load of arRP in our cohort.

Identification of causal mutations reaffirmed the role of *TULP1* in the pathogenesis of autosomal recessive RP and reiterates the heterogeneity associated with the disease phenotype. We compared the clinical phenotype of patients with arRP in PKRP084, PKRP111, PKRP122, and PKRP171 harboring the K489R allele reported by Iqbal et al. [83] with affected individuals in PKRP301, PKRP309, PKRP356, and PKRP367. However, we did not identify any distinction between the clinical phenotypes of affected individuals in these eight familial cases. All affected individuals in these familial cases manifested cardinal symptoms of RP, including attenuated retinal arteries and bone spicule–like pigment deposits accompanied by undetectable scotopic and photopic ERG responses. Identification of causal alleles responsible for arRP will help diagnostic efforts to identify carrier status in intermarried familial cases, and subsequent genetic counseling will help families make educated decisions regarding arranged marriages and screening for the status of newborns. In conclusion, we report seven familial cases harboring causal mutations in *TULP1*, including a common ancestral mutation that has now been identified in eight apparently unrelated familial cases.

## APPENDIX 1. PRIMER SEQUENCES FOR THE AMPLIFICATION OF *TULP1*.

To access the data, click or select the words "Appendix 1."

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