Published in final edited form as:
Hum Mutat. 2001 ; 17(1): 42–51. doi:10.1002/1098-1004(2001)17:1<42::AID-HUMU5>3.0.CO;2-K.

Prevalence of Mutations Causing Retinitis Pigmentosa and Other Inherited Retinopathies

Melanie M. Sohocki[1], **Stephen P. Daiger**[1,2], **Sara J. Bowne**[1], **Joseph A. Rodriquez**[3], **Hope Northrup**[3], **John R. Heckenlively**[4], **David G. Birch**[5], **Helen Mintz-Hittner**[2], **Richard S. Ruiz**[2], **Richard A. Lewis**[6], **David A. Saperstein**[7], and **Lori S. Sullivan**[1,2,*]

1*Human Genetics Center, School of Public Health, University of Texas-Houston Health Science Center, Houston, Texas*

2*Department of Ophthalmology and Visual Science, Medical School, University of Texas-Houston Health Science Center, Houston, Texas*

3*Department of Pediatrics, Medical School, University of Texas-Houston Health Science Center, Houston, Texas*

4*Jules Stein Eye Institute, University of California, Los Angeles, California*

5*Retina Foundation of the Southwest, Dallas, Texas*

6*Departments of Ophthalmology and Human and Molecular Genetics, Baylor College of Medicine, Houston, Texas*

7*Department of Ophthalmology, University of Washington, Seattle, Washington*

Abstract

Inherited retinopathies are a genetically and phenotypically heterogeneous group of diseases affecting approximately one in 2000 individuals worldwide. For the past 10 years, the Laboratory for Molecular Diagnosis of Inherited Eye Diseases (LMDIED) at the University of Texas-Houston Health Science Center has screened subjects ascertained in the United States and Canada for mutations in genes causing dominant and recessive autosomal retinopathies. A combination of single strand conformational analysis (SSCA) and direct sequencing of five genes (rhodopsin, peripherin/*RDS*, *RP1*, *CRX*, and *AIPL1*) identified the disease-causing mutation in approximately one-third of subjects with autosomal dominant retinitis pigmentosa (adRP) or with autosomal dominant cone-rod dystrophy (adCORD). In addition, the causative mutation was identified in 15% of subjects with Leber congenital amaurosis (LCA). Overall, we report identification of the causative mutation in 105 of 506 (21%) of unrelated subjects (probands) tested; we report five previously unreported mutations in rhodopsin, two in peripherin/RDS, and one previously unreported mutation in the cone-rod homeobox gene, *CRX*. Based on this large survey, the prevalence of disease-causing mutations in each of these genes within specific disease categories is estimated. These data are useful in estimating

*Correspondence to: Lori S. Sullivan, Ph.D., P.O. Box 20334, Houston, TX 77225-0334. E-mail: lsullivan@sph.uth.tmc.edu.
Communicated by Mark H. Paalman

DATABASES:
RHO – OMIM: 180380; GDB:120347; GenBank: U49742 (cDNA); HGMD: RHO
RDS – OMIM: 179605; GDB:118863; GenBank: NM_000322 (cDNA); HGMD: RDS
CRX – OMIM: 602225, 120970 (CORD2); GDB:9836957, GenBank: AF024711 (cDNA); HGMD: CRX
AIPL1 – OMIM: 604392, 604393 (LCA4); GDB:10029257; GenBank AF148864 (cDNA)
RP1 – OMIM: 603937, 180100; GDB:120352; GenBank; AF143222 (cDNA); HGMD: RP1; http://www.sph.uth.tmc.edu/RetNet/ (RetNet)

the frequency of specific mutations and in selecting individuals and families for mutation-specific studies.

Keywords

mutation analysis; retinal disorder; rhodopsin; RHO; peripherin; RDS; CRX; AIPL1; retinitis pigmentosa; RP7; RP4; cone-rod dystrophy; CORD2; Leber congenital amaurosis; LCA4; inherited retinopathy; RPI

INTRODUCTION

To date, over 120 loci for inherited retinal degeneration have been identified, and 56 of the associated genes have been cloned (RetNet, http://www.sph.uth.tmc.edu/RetNet/). Retinal disorders are also phenotypically heterogeneous, such that a single mutation may be associated with substantially different phenotypes within a family or between families, and different mutations within the same gene can cause substantially different retinal disorders. For example, mutations in one gene, peripherin/*RDS* (RDS; MIM# 179605), have been associated with several forms of inherited retinal degeneration, including cone-rod dystrophy, cone dystrophy, foveal dystrophy, and retinitis pigmentosa [Weleber et al., 1993; Wells et al., 1993; Keen et al., 1994; Nakazawa et al., 1994, 1996]. This clinical heterogeneity has made the molecular diagnosis of inherited eye diseases complicated; moreover, it has made identification of the underlying molecular cause of retinopathy within individual families an essential component of clinical research. If the gene defect causing the inherited retinopathy of a patient is identified, then prenatal diagnosis, a more accurate prognosis, and more accurate genetic counseling may be offered. In addition, several gene-specific and mutation-specific treatments for inherited retinal disorders have been proposed [Lewin et al., 1998; Frasson et al., 1999].

For the past decade, the Laboratory for Molecular Diagnosis of Inherited Eye Diseases (LMDIED, CLIA#45D0935007) at The University of Texas-Houston Health Science Center has tested over 500 unrelated subjects (probands) with inherited retinal disorders who were ascertained within Canada and the United States. The complete coding sequences of rhodopsin (RHO; MIM# 180380), peripherin/*RDS*, *CRX* (MIM# 602225), and *AIPL1* (MIM# 604392) were assayed in all samples by SSCA, followed by sequencing of variants. In addition, because disease-causing mutations in the *RP1* gene (MIM# 603937) appear to cluster in one region of exon 4 [Bowne et al., 1999], that region was assayed by SSCA in all patient samples, and all variants were sequenced. We report identification of the disease-causing mutation in roughly one-third of subjects with autosomal dominant retinitis pigmentosa (adRP) or with autosomal dominant cone-rod dystrophy (adCORD) (Table 1). In addition, mutations were identified in approximately 15% of subjects with Leber congenital amaurosis (LCA).

MATERIALS AND METHODS

Subjects

Informed consent was obtained from all adult subjects, who were ascertained in the United States and Canada. Ethnicity of subjects could not be determined in most cases, as all samples were obtained under institutional rules of confidentiality. However, the population origin for these subjects is largely Caucasian of European ancestry. All tested individuals with disease-causing mutations received clinical evaluations by at least one of the co-authors, and in some instances, by two co-authors jointly.

DNA Isolation

DNA was isolated from peripheral blood using the Puregene DNA extraction kit (Gentra, Minneapolis, MN), in accordance with the manufacturer's instructions. A working stock for mutation analysis was stored at 4°C, and the primary sample was stored separately at −70°C. All mutations identified by SSCA and direct sequencing of the working stock were confirmed by direct sequencing of the primary DNA sample.

SSCP Analysis

Genomic DNA samples from subjects were screened by SSCA, using published PCR primer sequences and conditions: rhodopsin [Daiger et al., 1997], peripherin/*RDS* [Daiger et al., 1997], *CRX* [Sohocki et al., 1998], *RP1* [Bowne et al., 1999], and *AIPL1* [Sohocki et al., 2000].

DNA Sequencing

After an SSCA variant was identified, a PCR reaction was performed under the same conditions as for SSCA. The amplified fragment was then treated with shrimp alkaline phosphatase and exonuclease I (USB, Cleveland, OH). Direct sequencing was performed with either the AmpliCycle sequencing kit (PE Biosystems) and a primer end-labeled with ^{33}P-ATP followed by autoradiography, or the BigDye Terminator Sequencing Kit (PE Biosystems) on an ABI Prism 310 automated sequencer according to the manufacturer's protocols.

Peripherin/RDS Haplotype Identification

For haplotype identification of the peripherin/*RDS* exon 3 polymorphisms, DNA was amplified incorporating ^{32}P-dCTP with a biotinylated forward primer (5′-TTGGGCTGCTACCTACAG-3′) and an unbiotinylated reverse primer (5′-AGACTTTCGGAGTTGGATGAG-3′) and standard cycling conditions. Individual strands were separated with Dynabeads (DYNAL, Lake Success, NY) according to manufacturer's protocols and were separated overnight on 0.4X MDE (Biowhittaker, Rock-land, ME) gels.

RESULTS

Likely disease-causing mutations were identified in 105 of the 506 total probands tested, or in approximately 21% of samples. The frequency of mutations identified in autosomal dominant retinopathies was considerably higher—approximately one-third of adRP and one-third of autosomal dominant retinal degeneration with cone involvement were explained by mutations identified in this study.

Retinitis Pigmentosa

Rhodopsin—Rhodopsin mutations were identified in 53 probands from 206 adRP families (26%), two from isolated probands with RP, and four from individuals with RP of unknown inheritance pattern (Table 2A). As expected, the Pro23His rhodopsin mutation was the most frequent, representing 41% of rhodopsin mutations and causing adRP in 22 of 206 (11%) of subjects. The second most common mutation was Arg135Trp, found in 5 (3%) of adRP families. In addition to published mutations, five previously unreported disease-causing rhodopsin mutations were identified, each confirmed by direct genomic sequencing in at least one independently collected DNA sample.

Pro170Arg—The Pro170Arg mutation segregated with RP in three affected individuals of RFS153, and was not observed in any of the other 1,000 chromosomes tested. This nonconservative substitution replaces the neutral, hydrophobic, rigid ring of proline with a large, basic arginine residue within the fourth transmembrane region of rhodopsin.

Cys185Arg—The Cys185Arg mutation segregated with the retinitis pigmentosa of two adRP families, RFS075 and RFS088, and was not observed in any other probands tested. The cysteine at this position is conserved in lamprey, chicken, bovine, and human rhodopsin [Okano et al., 1992].

Pro210Leu—A Pro210Leu mutation was identified in the affected proband of UTAD088 and was not observed in the other individuals tested. This mutation is nonconservative, substituting leucine for the rigid ring of proline at this position within the fifth transmembrane region of rhodopsin. As proline is known to be important in folding the peptide chain, this mutation is likely to alter the secondary structure of the protein.

Leu318del—A 3 base pair deletion was identified in an isolated individual with RP, UTAD338. The deletion alters amino acids 318 and 319, deleting the leucine at position 318, and causing the threonine at position 319 to be replaced by a proline. The threonine at position 319 is highly conserved in lamprey, chicken, bovine, and human rhodopsin [Okano et al., 1992].

Peripherin/RDS—Disease-causing mutations in peripherin/RDS were identified in approximately 8% (17 of 206) of the adRP probands. In addition, mutations were identified in two isolated RP cases (Table 2B). Two previously unreported mutations were also identified.

Tyr141Cys—A Tyr141Cys mutation segregated with the retinitis pigmentosa in affected individuals of family BCMAD033 and in none of the other 1,000 chromosomes tested. The tyrosine at this position is conserved in human, bovine, and murine peripherin/rds [Connell et al., 1991].

Gln178Arg—The Gln178Arg mutation was observed only in the affected proband of family UTAD185. The glutamine at residue 178 of peripherin/RDS is conserved in human, bovine, and murine peripherin/rds [Connell et al., 1991].

RP1—The majority of disease-causing RP1 mutations detected to date cluster in a region of exon 4 [Bowne et al., 1999; Grimsby, 2000]; therefore, 150 of the probands were assayed by SSCA in this region only. The remaining 56 probands are of large adRP families and were tested for mutations in the complete RP1 gene by SSCA. Five previously reported RP1 mutations were identified by LMDIED in eight of the 206 adRP probands, or in about 4% of adRP tested (Table 2C).

Cone-rod homeobox gene, CRX—CRX mutations were identified in two families diagnosed with adRP, RFS087, and UTAD341. The proband of RFS087 was heterozygous for the Arg41Gln mutation reported previously [Swain et al., 1997] in the proband of a family with autosomal dominant cone-rod dystrophy. Following identification of the mutation, detailed clinical evaluations in this and other family members indicated that the phenotype in RFS087 is more accurately described as a late-onset, slowly progressing, mild form of cone-rod dystrophy [Tzekov et al., 2000].

Another previously unreported mutation, Arg115Gln (G344A, CGG→CAG), was identified in the affected proband of UTAD341. This mutation was not identified in 50 normal control individuals or in any of the other 1,000 chromosomes tested. The arginine at this position is conserved among human, bovine, and murine Crx, and in human CRX and OTX-1, and OTX-2, two members of the same protein family [Chen et al., 1997]. Additional clinical evaluations are necessary to determine if the affected individuals of UTAD341 have a retinal degeneration phenotype similar to the family with the Arg41Gln mutation and to confirm the phenotype in the UTAD341 family as “retinitis pigmentosa.”

Retinal Disorders With Cone Involvement

The retinal disorders in this category include those with clinical diagnoses of cone-rod dystrophy, cone degeneration, macular degeneration, and Bardet-Biedl disease (Table 3). Six previously reported mutations were identified as the cause of retinal degeneration in 12 families whose retinal disorder included cone degeneration. No rhodopsin mutations were identified in this category.

Leber Congenital Amaurosis (LCA)

Homozygous or compound-heterozygous mutations were identified in three of 25 (~12%) probands with recessive or isolated LCA. In addition, a heterozygous CRX mutation was identified as the cause of autosomal dominant LCA in one family (Table 4). Therefore, the causative mutation was identified in approximately 15% (four of 27) of all subjects with a diagnosis of Leber congenital amaurosis.

Benign Variants

Several apparently benign coding sequence variants were identified in the current survey (Table 5). In addition, frequencies were determined for the haplotypes of peripherin/RDS codon 304/310/338 polymorphisms. The respective frequencies for the G/A/G, C/G/A, and C/ A/A haplotypes were 0.77, 0.09, and 0.13. Two unique haplotypes, C/A/G and G/A/A, were also identified in one individual each.

DISCUSSION

The purpose of this project was to determine the prevalence of disease-causing mutations in five genes known to cause inherited retinopathy: rhodopsin, peripherin/RDS, RP1, CRX, and AIPL1. Mutation testing was performed in over 500 subjects in the broad diagnostic categories of either retinitis pigmentosa without apparent cone involvement or retinal degeneration with cone involvement. Patients were further classified by mode of inheritance and detailed clinical findings. Patients in the study were from families ascertained in the United States or Canada. In addition to providing useful clinical information for the patients and families involved in the study, mutation screening in this population offers several further benefits. First, this survey permits estimation of the relative prevalences (relative to each disease category) for mutations within each gene and for each observed mutation. This information is useful in determining the gene-specific and mutation-specific diagnostic and treatment needs within this population. Second, we report eight novel disease-causing mutations which contribute to the overall allelic variability at these loci. Third, we report several benign sequence variants within these genes, and their respective frequencies. These data will assist other diagnostic laboratories in distinguishing disease-causing mutations from benign variants. Finally, families and patients with specific mutations, identified in this study by confidential numbers, may be available for further study. Access to these subjects, with appropriate consent and maintenance of confidentiality, is available through the clinicians participating in the survey.

These data reinforce the heterogeneity of inherited retinopathies and the need for molecular diagnostics. For example, a single peripherin/*RDS* splice-site mutation, IVS2+3A>T, was identified as the cause of retinopathy in eight families; the phenotype in these families ranges from retinitis pigmentosa to macular degeneration. Further, although our assays may have missed some mutations, our data indicate that the inherited retinal degeneration genes that were not screened or have not yet been identified may account for approximately two-thirds of inherited retinopathy in these diagnostic categories. The combination of the heterogeneity of inherited retinal disorders and the developing studies involving gene-specific or mutation-specific treatments for these disorders makes identification of the remaining genes and accurate molecular diagnosis of these disorders even more important.

Acknowledgements

We express our sincere gratitude to all of the families who participated in our survey. We thank the following individuals for expert technical assistance: Noelle Agan, Melanie An-drews-Casal, Heather Ferguson, Alex Gannon, Sharon Guilford, Patricia Hamilton, Dennis Hoffman, Dianna Hughbanks-Wheaton, Jill Overseer, Jill Sawyer, and Myla Tuazon.

Contract grant sponsors: Foundation Fighting Blindness; George Gund Foundation; William Stamps Farish Fund; M.D. Anderson Foundation; John S. Dunn Research Foundation; Contract grant sponsor: National Eye Institute-National Institutes of Health; Contract grant numbers: EY07142; EY05235.

References

Antinolo G, Sanchez B, Borrego S, Rueda T, Chaparro P, Cabeza JC. Identification of a new mutation at codon 171 of rhodopsin gene causing autosomal dominant retinitis pigmentosa. Hum Mol Genet 1994;3:1421. [PubMed: 7987326]

Bowne SJ, Daiger SP, Hims MM, Sohocki MM, Malone KA, McKie AB, Heckenlively JR, Birch DG, Inglehearn CF, Bhattacharya SS, Bird A, Sullivan LS. Mutations in the RP1 gene causing autosomal dominant retinitis pigmentosa. Hum Mol Genet 1999;8:2121–2128. [PubMed: 10484783]

Chen S, Wang Q, Nie Z, Sun H, Lennon G, Copeland NG, Gilbert DJ, Jenkins NA, Zack DJ. Crx, a novel otx-like paired-homeodomain protein, binds to and transactivates photoreceptor cell-specific genes. Neuron 1997;19:1017–1030. [PubMed: 9390516]

Connell G, Bascom R, Molday L, Reid D, McInnes RR, Molday RS. Photoreceptor peripherin is the normal product of the gene responsible for retinal degeneration in the *rds* mouse. Proc Natl Acad Sci USA 1991;38:723–726. [PubMed: 1992463]

Daiger, SP.; McGuire, RE.; Sullivan, LS.; Sohocki, MM.; Blanton, SH.; Humphries, P.; Green, ED.; Mintz-Hittner, H.; Heckenlively, JR. Progress in positional cloning of RP10 (7q31.3), RP1 (8q11-q21), and VMD1 (8q24). In: LaVail, MM.; Hollyfield, JG.; Anderson, RE., editors. Degenerative retinal diseases. New York: Plenum Press; 1997. p. 277-294.

Dryja TP, McGee TL, Reichel E, Hahn LB, Cowley GS, Yandell DW, Sandberg MA, Berson EL. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature 1990;343:364. [PubMed: 2137202]

Dryja TP, Hahn LB, Cowley GS, McGee TL, Berson EL. Mutation spectrum of the rhodopsin gene among subjects with autosomal dominant retinitis pigmentosa. Proc Natl Acad Sci USA 1991;88:9370–9374. [PubMed: 1833777]

Farrar GJ, Findlay JB, Kumar-Singh R, Kenna P, Humphries MM, Sharpe E, Humphries P. Autosomal dominant retinitis pigmentosa: a novel mutation in the rhodopsin gene in the original 3q linked family. Hum Mol Genet 1992;1:769. [PubMed: 1302614]

Feist RM, White MF Jr, Skalka H, Stone EM. Choroidal neovascularization in a patient with adult foveomacular dystrophy and a mutation in the retinal degeneration slow gene. Am J Ophthalmol 1994;118:259–260. [PubMed: 7519821]

Fishman GA, Stone E, Gilbert LD, Vandenburgh K, Sheffield VC, Heckenlively JR. Clinical features of a previously undescribed codon 216 (proline to serine) mutation in the peripherin/retinal degeneration slow gene in autosomal dominant retinitis pigmentosa. Ophthalmology 2000;101:1409–1421. [PubMed: 8058286]

Frasson M, Sahel JA, Fabre M, Simonutti M, Dreyfus H, Picaud S. Retinitis pigmentosa: rod photoreceptor rescue by a calcium-channel blocker in the rd mouse. Nat Med 1999;5:1183–1187. [PubMed: 10502823]

Freund CL, Gregory-Evans CY, Furukawa T, Papaioannou M, Looser J, Ploder L, Bellingham J, Ng D, Herbrick JA, Duncan A, Scherer SW, Tsui LC, Loutradis-Anagnostou A, Jacobson SG, Cepko CL, Bhattacharya SS, McInnes RR. Cone-rod dystrophy due to mutations in a novel photoreceptor-specific homeobox gene (CRX) essential for maintenance of the photoreceptor. Cell 1997;91:543–553. [PubMed: 9390563]

Fuchs S, Kranich H, Denton MJ, Zrenner E, Bhattacharya SS, Humphries P, Gal A. Three novel rhodopsin mutations (C110F, L131P, A164V) in subjects with autosomal dominant retinitis pigmentosa. Hum Mol Genet 1994;3:1203. [PubMed: 7981701]

Grimsby JL, Adams SM, McGee TL, Pierce EA, Berson EL, Dryja TP. Mutations in the RP1 gene causing dominant retinitis pigmentosa. Invest Opthalmol Vis Sci 2000;41:S192.

Inglehearn CF, Keen TJ, Bashir R, Jay M, Fitzke F, Bird AC, Crombie A, Bhattacharya S. A completed screen for mutations of the rhodopsin gene in a panel of subjects with autosomal dominant retinitis pigmentosa. Hum Mol Genet 1992;1:41–45. [PubMed: 1301135]

Jacobson SG, Cideciyan AV, Bascom RA, McInnes RR, Sheffield VC, Stone EM. Variable expression of retinitis pigmentosa in patients with digenic inheritance of peripherin/RDS and ROM-1 gene mutations. Invest Ophthalmol Vis Sci 1995;36:913.

Kajiwara K, Berson EL, Dryja TP. Screen for mutations in the entire coding sequence of the human RDS/peripherin gene in patients with hereditary retinal degenerations. Invest Ophthalmol Vis Sci 1992;33:1149.

Keen TJ, Inglehearn CF, Lester DH, Bashir R, Jay M, Bird AC, Jay B, Bhattacharya SS. Autosomal dominant retinitis pigmentosa: four new mutations in rhodopsin, one of them in the retinal attachment site. Genomics 1991;11:199. [PubMed: 1765377]

Keen TJ, Inglehearn CF, Kim R, Bird AC, Bhattacharya S. Retinal pattern dystrophy associated with the 4 bp insertion at codon 140 in the RDS-peripherin gene. Hum Mol Genet 1994;3:367–368. [PubMed: 8004111]

Keen TJ, Inglehearn CF. Mutations and polymorphisms in the human peripherin-RDS gene and their involvement in inherited retinal degeneration. Hum Mutat 1996;8:297–303. [PubMed: 8956033]

Lewin AS, Dresner KA, Hauswirth WW, Nishikawa S, Yasumura D, Flannery JG, LaVail MM. Ribozyme rescue of photoreceptor cells in a transgenic rat model of autosomal dominant retinitis pigmentosa. Nat Med 1998;4:967–971. [PubMed: 9701253]

Macke JP, Davenport CM, Jacobson SG, Hennessey JC, Gonzalez-Fernandez F, Conway BP, Heckenlively J, Palmer R, Maumenee IH, Sieving P, Gouras P, Good W, Nathans J. Identification of novel rhodopsin mutations responsible for retinitis pigmentosa: implications for the structure and function of rhodopsin. Am J Hum Genet 1993;53:80–89. [PubMed: 8317502]

Meins M, Gruning G, Blankenagel A, Krastel H, Reck B, Fuchs S, Schwinger E, Gal A. Heterozygous ‘null allele’ mutation in the human peripherin/RDS gene. Hum Mol Genet 1993;2:2181–2182. [PubMed: 8111389]

Nakazawa M, Kiawa E, Chida Y, Tamai M. Asn244His mutation of the peripherin/RDS gene causing autosomal dominant cone-degeneration. Hum Mol Genet 1994;3:1195–1196. [PubMed: 7981698]

Nakazawa M, Kiawa E, Chida Y, Wada Y, Shiono T, Tamai M. Autosomal dominant cone-rod retinal dystrophy associated with mutations in codon 244 (Asn244His) and codon 184 (Tyr184Ser) of the peripherin/RDS gene. Arch Ophthalmol 1996;114:72–78. [PubMed: 8540854]

Okano T, Kojima D, Fukada Y, Shichida Y, Yoshizawa T. Primary structures of chicken cone visual pigments: vertebrate rhodopsins have evolved out of cone visual pigments. Proc Natl Acad Sci USA 1992;89:5932–5936. [PubMed: 1385866]

Pierce EA, Quinn T, Meehan T, McGee TL, Berson EL, Dryja TP. Mutations in a gene encoding a new oxygen-regulated photoreceptor protein cause dominant retinitis pigmentosa. Nat Genet 1999;22:248–254. [PubMed: 10391211]

Robinson PR, Cohen GB, Zhukovsky EA, Oprian DD. Constitutively active mutants of rhodopsin. Neuron 1992;9:719–725. [PubMed: 1356370]

Rodriguez JA, Herrera CA, Birch DG, Daiger SP. A leucine to arginine amino acid substitution at codon 46 of rhodopsin is responsible for a severe form of autosomal dominant retinitis pigmentosa. Hum Mutat 1993;2:205. [PubMed: 8364589]

Sheffield VC, Fishman GA, Beck JS, Kimura AE, Stone EM. Identification of novel rhodopsin mutations associated with retinitis pigmentosa by GC-clamped denaturing gradient gel electrophoresis. Am J Hum Genet 1991;49:699–706. [PubMed: 1897520]

Sohocki MM, Sullivan LS, Mintz-Hittner HA, Birch D, Heckenlively JR, Freund CL, McInnes RR, Daiger SP. A range of clinical phenotypes associated with mutations in CRX, a photoreceptor transcription-factor gene. Am J Hum Genet 1998;63:1307–1315. [PubMed: 9792858]

Sohocki MM, Bowne SJ, Sullivan LS, Blackshaw S, Cepko CL, Payne AM, Bhattacharya SS, Khaliq S, Mehdi SQ, Birch DG, Harrison WR, Elder FFB, Heckenlively JR, Daiger SP. Mutations in a new

photoreceptor-pineal gene on 17p cause Leber congenital amaurosis. Nat Genet 2000a;24:79–83. [PubMed: 10615133]

Sohocki MM, Perrault I, Leroy BP, Payne AM, Dharmaraj S, Bhattacharya SS, Kaplan J, Maumenee IH, Koenekoop R, Meire FM, Birch DG, Heckenlively JR, Daiger SP. Prevalence of AIPL1 mutations in inherited retinal degenerative diseases. Mol Genet Metab 2000b;70:142–150. [PubMed: 10873396]

Stone EM, Vandenburgh K, Kimura AE, Lam BL, Fishman GA, Heckenlively JR, Castillo TA, Sheffield VC. Novel mutations in the peripherin (RDS) and rhodopsin genes associated with autosomal dominant retinitis pigmentosa (ADRP). Invest Opthalmol Vis Sci 1993;34:1149.

Sullivan JM, Scott KM, Falls HP, Richards JE, Sieving PA. A novel mutation at the retinal binding site (Lys296Met) in ADRP. Invest Ophthalmol Vis Sci 1993;34:1149.

Sullivan LS, Guilford SR, Birch DG, Daiger SP. A novel splice site mutation in the gene for peripherin/RDS causing dominant retinal degeneration. Invest Ophthalmol Vis Sci 1996;37:S1145.

Sullivan LS, Heckenlively JR, Bowne SJ, Zuo J, Hide WA, Gal A, Denton M, Inglehearn CF, Blanton SH, Daiger SP. Mutations in a novel retina-specific gene cause autosomal dominant retinitis pigmentosa. Nat Genet 1999;22:255–259. [PubMed: 10391212]

Sung CH, Davenport CM, Hennessey JC, Maumenee IH, Jacobson SG, Heckenlively JR, Nowakowski R, Fishman G, Gouras P, Nathans J. Rhodopsin mutations in autosomal dominant retinitis pigmentosa. Proc Natl Acad Sci USA 1991;88:6481. [PubMed: 1862076]

Swain PK, Chen S, Wang Q, Affatigato LM, Coats CL, Brady KD, Fishman GA, Jacobson SG, Swaroop A, Stone E, Sieving PA, Zack DJ. Mutations in the cone-rod homeobox gene are associated with cone-rod dystrophy photoreceptor degeneration. Neuron 1997;19:1329–1336. [PubMed: 9427255]

Tzekov RT, Sohocki MM, Daiger SP, Birch DG. Visual phenotype in subjects with the Arg41Gln and Ala196+1bp mutations in the CRX gene. Ophthal Genet 2000;21:89–99.

Vaithinathan R, Berson EL, Dryja TP. Further screening of the rhodopsin gene in subjects with autosomal dominant retinitis pigmentosa. Genomics 1994;21:461–463. [PubMed: 8088850]

Weleber RG, Carr RE, Murphet WH, Sheffield VC, Stone EM. Phenotypic variation including retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/ RDS gene. Arch Ophthalmol 1993;111:1531–1542. [PubMed: 8240110]

Wells J, Wroblewski J, Keen J, Inglehearn C, Jubb C, Eckstein A, Jay M, Arden G, Bhattacharya S, Fitzke F, Bird A. Mutations in the human retinal degeneration slow (RDS) gene can cause either retinitis pigmentosa or macular dystrophy. Nat Genet 1993;3:213–218. [PubMed: 8485576]

Wroblewski JJ, Wells JA 3rd, Eckstein A, Fitzke F, Jubb C, Keen TJ, Inglehearn C, Bhattacharya S, Arden GB, Jay M, et al. Macular dystrophy associated with mutations at codon 172 in the human retinal degeneration slow gene. Ophthalmology 1994;101:12–22. [PubMed: 8302543]

TABLE 1

Summary of Probands Whose Causative Mutation Was Identified in This Study

Diagnosis	Mode of inheritance	Total tested	Rhodopsin	Peripherin/*RDS*	*RP1*	*CRX*	*AIPL1*
RP[a]	Autosomal dominant	206	53	17	8	2	0
	Isolated/recessive	138	2	0	0	0	0
	Unknown[b]	79	4	2	0	0	0
RD w/cone	Autosomal dominant	34	0	7	0	3	2
	Isolated/recessive	17	0	2	0	0	0
	Unknown[b]	15	0	0	0	0	0
LCA	Autosomal dominant	2	0	0	0	1	0
	Isolated/recessive	25	0	0	0	0	3

[a] RP, retinitis pigmentosa; RD w/cone, retinal disorder with cone involvement; LCA, Leber congential amaurosis; *CRX*, cone-rod homeobox gene; *AIPL1*, aryl-hydrocarbon interacting protein-like 1.

[b] Family history unavailable.

TABLE 2A

Summary of Rhodopsin Mutations Identified in Families With Retinitis Pigmentosa (in Codon Order)

Diagnosis	Mutation/predicted consequence	Family identifier	cDNA[a]	Reference
ad RP	Pro23His	22 Families[b]	68C>A, CCC→CAC	Dryja et al. [1990]
ad RP	Leu46Arg	RFS004	137T>G, CTC→CGG	Rodriguez et al. [1993]
ad RP	Leu57Arg	UTAD070	170C>G, CCC→CGC	Inglehearn et al. [1992]
ad RP	Gly106Trp	UTAD013	316G>T, GGG→TGG	Sung et al. [1991]
ad RP	Gly106Arg	RFS072, RFS086	318A>G, GGA→GGG	Inglehearn et al. [1992]
ad RP	Cys110Phe	RFS036	329G>T, TGC→TTC	Fuchs et al. [1994]
ad RP	Arg135Trp	5 Families[c]	403C>T, CGG→TGG	Sung et al. [1991]
ad RP	Ala164Val	RFS163	491C>T, GCG→GTG	Fuchs et al. [1994]
ad RP	Pro170Arg	RFS153	509C>G, CCC→CGC	Present study
ad RP	Pro171Ser	RFS049	511C>T, CCA→TCA	Vatithinathan et al. [1994]
ad RP	Pro171Gln	UTAD096	512C>A, CCA→CAA	Antiñolo et al. [1994]
ad RP	Glu181Lys	UTAD089, UIC17	541G>A, GAG→AAG	Dryja et al. [1991]
ad RP	Cys185Arg	RFS075, RFS089	553T>C, TGC→CGC	Present study
ad RP	Asp190Asn	RFS003	568G>A, GAC→AAC	Keen et al. [1991]
ad RP	Met207Arg	TCDM	620T>G, ATG→AGG	Farrar et al. [1992]
ad RP	Pro210Leu	UTAD088	629C>T, CCT→CTT	Present study
ad RP	His211Arg	UTAD022	632A>G, CAC→CGC	Macke et al. [1993]
ad RP	Ser270Arg	UTAD042	C810A, AGC→AGA	Daiger et al. [1997]
ad RP	Lys296Asn	UTAD396	888G>T, AAG→AAT	Present study
ad RP	Frameshift after Glu332	UTAD072	995-1011del	Daiger et al. [1997]
ad RP	Pro347Ala	UTAD407	1039C>G, CCG→GCG	Stone et al. [1993]
ad RP	Pro347Leu	UTAD188, UTAD140	1040C>T, CCG→CTG	Dryja et al. [1990]
ad RP	Pro347Thr	UTAD081	1039C>A, CCG→ACG	Daiger et al. [1997]
RP, isolated	Pro180Ala	UTAD052	538C>G, CCC→GCC	Daiger et al. [1997]
RP, isolated	Leu318del	UTAD338	953-955del	Present study
RP[d]	Arg135Leu	UTAD264, UTAD332	404G>T, 405G>T, CGG→CTT	Sung et al. [1991]
RP[d]	Arg135Trp	RFS105	403C>T, CGG→TGG	Sung et al. [1991]
RP, sectoral[d]	Thr17Met	RFS160	50C>T, ACG→ATG	Sheffield et al. [1991]

[a] cDNA sequence numbering, counting the first nucleotide of the first codon as 1. None of these mutations were identified in 50 unaffected control individuals.

[b] BCMAD032, RFS001, RFS008, RFS010, RFS023, RFS025, RFS037, RFS069, RFS071, RFS136, RFS159, RFS162, UIC15, UTAD010, UTAD018, UTAD043, UTAD084, UTAD085, UTAD109, UTAD230, UTAD414, UTAD437.

[c] RFS096, RP01B, UTAD120, UTAD159, UTAD163.

[d] Family history unavailable.

TABLE 2B

Summary of Peripherin/RDS Mutations Identified in Families With Retinitis Pigmentosa

Diagnosis	Mutation/predicted consequence	Family identifier	cDNA[a]	Reference
ad RP	Arg46Ter	UTAD399	136C>T, CGA→TGA	Meins et al. [1993]
ad RP	Leu126Arg	UTAD280	377T>G, CTG→CGG	Kajiwara et al. [1992]
ad RP	Arg172Gln	UTAD396	516G>T, AAG→AAT	Wells et al. [1993]
ad RP	Leu185Pro	UTAD215	554T>C, CTG→CCG	Kajiwara et al. [1992]
ad RP	Val206-209del	UTAD023	616-627del	Keen et al. [1996]
ad RP	Pro210Arg	4 Families[b]	629C>G, CCT→CGT	Feist et al. [1994]
ad RP	Pro216Leu	RFS070, RFS058	647C>T, CCT→CTT	Kajiwara et al. [1992]
ad RP	Pro216Ser	UTAD095	646C>T, CCG→TCT	Fishman et al. [1994]
ad RP	Gly266Asp	UTAD056, UTAD058	797G>A, GGT→GAT	Kajiwara et al. [1992]
ad RP	IVS2+3 A>T	3 Families[c]	1068+3A→T	Sullivan et al. [1996]
RP vs. AFMD	Tyr141Cys	BCMAD033	422A>G, TAC→TGC	Present study
RP[d]	Gln178Arg	UTAD185	533A>G, CAG→CGG	Present study
RP[d]	Pro210Arg	UTAD313	629C>G, CCT→CGT	Feist et al. [1994]

[a] cDNA sequence numbering, counting the first nucleotide of the first codon as 1. None of these mutations were identified in 50 unaffected control individuals.

[b] RFS079, RFS152, UTAD174, UTAD379.

[c] RFS027, RFS055, RFS083.

[d] Family history unavailable.

TABLE 2C

Summary of RP1 Mutations Identified in Families With Retinitis Pigmentosa

Diagnosis	Mutation/predicted consequence	Family identifier	cDNA[a]	Reference
ad RP	Arg677Ter	RFS137, UTAD103	2029C>T, CGA→TGA	Sullivan et al. [1999]; Pierce et al. [1999]; Bowne et al. [1999]
ad RP	Gly723Ter	UTAD411	2167G>T, GGA→TGA	Grimsby et al. [2000]
ad RP	Frameshift after Ile725	UTAD309	2169-2170insG	Bowne et al. [1999]
ad RP	Frameshift after Leu762	3 Families[b]	2285-2289del	Pierce et al. [1999]; Bowne et al. [1999]
ad RP	Frameshift after Gly723	RFS103	2303del	Bowne et al. [1999]

[a] cDNA sequence numbering, counting the first nucleotide of the first codon as 1. None of these mutations were identified in 50 unaffected control individuals.

[b] UTAD029, UTAD039, UTAD351.

TABLE 3

Summary of Mutations Identified in Retinopathy Subjects With Cone Involvement

Mutation/predicted consequence	Diagnosis	Family identifier	cDNA[a]	Reference
RDS Arg172Trp	ad CD[b], progressive	RFS139	514C>T, CGG→TGG	Wroblewski et al. [1994]
RDS Arg13Trp	Bardet Biedl	UTAD087	37C>T, CGG→TGG	Jacobson et al. [1995]
RDS Leu45Phe	CORD, isolated	UTAD064	133C>T, CTC→TTC	Jacobson et al. [1995]
RDS IVS2+3 A>T	ad MD[c]	Five families[d]	1068+3A→T	Sullivan et al. [1996]
CRX Glu80Ala	ad CORD	UTAD148, UTAD237	238A>C, GAG→GCG	Freund et al. [1997]
CRC Frameshift after Ala196	ad CORD	RFS014	585insC	Sohocki et al. [1998]
AIPL 1 Pro 351-354del	ad CORD	UTAD231, UTAD907	del1053-1064	Sohocki et al. [2000b]

[a] cDNA sequence numbering, counting the first nucleotide of the first codon as 1. These mutations were not present in 50 unaffected control individuals.

[b] adCORD, autosomal dominant cone-rod dystrophy; adCD, autosomal dominant cone degeneration; adMD, autosomal dominant macular degeneration.

[c] Macular degeneration with peripheral involvement.

[d] RFS091, RFS142, RFS156, RFS161, UTAD207.

TABLE 4

Summary of Mutations Identified in Retinopathy Subjects With Leber Congenital Amaurosis

Mutation/predicted consequence	Diagnosis	Family identifier	cDNA[a]	Reference
AIPL1 Trp278Ter	LCA	RFS121	834G>A, TGG→TGA	Sohocki et al. [2000a]
AIPL1 Frameshift after Ala336		RFS121	1008-1009del	Sohocki et al. [2000a]
AIPL1 Trp278Ter	ar LCA	RFS127	834G>A, TGG→TGA	Sohocki et al. [2000a]
AIPL1 Cys239Arg	ar LCA	RFS128	717T>C, TGC→CGC	Sohocki et al. [2000a]
CRX Leu146-149del	ad LCA	RFS900	438-449del	Sohocki et al. [1998]

[a] cDNA sequence numbering, counting the first nucleotide of the first codon as 1. None of these mutations were identified in 50 unaffected control individuals.

TABLE 5

Apparently Benign Coding Sequence Variants in This Population

Gene	Variant	cDNA	Evidence[a]	Frequency
Rhodopsin	GLy120Gly	360C>T (GGC→GGT)	2	.02
	Thr160Thr	480C>T (ACC→ACA)	2	<.01
	Ala173Ala	519C>T (GCC→GCT)	2	<.01
	Ser186Ser	558G>A (TCG→TCA)	2	<.01
	Ser297Ser	891C>T (AGC→AGT)	2	<.01
Peripherin/*RDS*	Val106Val	318C>T (GTC→GTT)	2	.26
	Glu304Gln	910G>C (GAG→GCT)	3 Keen et al. [1996]	.23
	Lys310Arg	929A>G (AAG→AGG)	3 Keen et al. [1996]	.10
	Gly336Gly	1008C>T (GGC→GGT)	2	<.01
	Gly338Asp	1014G>A (GGC→GAC)	3 Keen et al. [1996]	.22
RP1	Arg872His	2615G>A (CGT→CAT)	3 Sullivan et al. [1999]	.25
	Asn985Tyr	2953A>T (AAT→TAT)	3 Sullivan et al. [1999]	.46
	Arg1595Gln	4784G>A (CGG→CAG)	1	<.01
	Ala1670Thr	5008G>A (GCA→ACA)	3 Sullivan et al. [1999]	.22
	Ser1691Pro	5071T>C (TCT→CCT)	3 Sullivan et al. [1999]	.23
	Gln1725Gln	5175A>G (CAA→CAG)	3 Sullivan et al. [1999]	.20
	Cys2033Tyr	6098A>G (TAT→TGT)	3 Sullivan et al. [1999]	.46
	Leu808Pro	5423T>C (CTG→CCG)	1	.01
	Ile2122Ile	6366T>C (ATT→ATC)	2	<.01
CRX	His10Asp	28C>T (CAC→GAC)	2	<.01
	Val66Ile	196G>A (GTC→ATC)	1	<.01
	Gly122Asp	365G>A (GGC→GAC)	4	<.01
	Ala158Thr	472G>A (GCC→ACC)	3 Swain et al. [1997]	<.01
	Gly183Gly	538G>A (GGG→GGA)	2	<.01
	Ser199Ser	596C>T (TCC→TCT)	1	<.01
AIPL1	Phe37Phe	111T>C (TTT→TTC)	2	.02
	Ser78Ser	234C>T (TCC→TCT)	2	<.01
	Cys89Cys	287C>T (TGC→TGT)	2	.01
	Asp90His	268G>C (GAC→CAC)	1	.16
	Leu100Leu	300G>A (CTG→CTA)	2	.43
	His172His	516T>C (CAT→CAC)	2	<.01
	Pro217Pro	651G>A (CCG→CCA)	2	.39
	Asp255Asp	765T>C (GAT→GAC)	2	<.01

[a] Evidence that variant is benign: 1 = does not segregate with retinal disorder in one or more families; 2 = Silent substitution; 3 = published reference; 4 = variance identified in unaffected controls.