Title

Identification of the genetic determinants responsible for retinal degeneration in families of Mexican descent

Journal

Ophthalmic Genetics, 39(1)

ISSN

1381-6810

Authors

Villanueva, Adda
Biswas, Pooja
Kishaba, Kameron
et al.

Publication Date

2018-01-02

DOI

10.1080/13816810.2017.1373830

Peer reviewed

HHS Public Access

Author manuscript

Ophthalmic Genet. Author manuscript; available in PMC 2018 September 18.

Published in final edited form as:

Ophthalmic Genet. 2018 ; 39(1): 73–79. doi:10.1080/13816810.2017.1373830.

Identification of the genetic determinants responsible for retinal degeneration in families of Mexican descent

Adda Villanueva[#1,2], **Pooja Biswas**[#3,4], **Kameron Kishaba**[4], **John Suk**[4], **Keerti Tadimeti**[4], **P.B Raghavendra**[3], **Karine Nadeau**[1,2], **Bruno Lamontagne**[1,2], **Lambert Busque**[1,2], **Steve Geoffroy**[5,6], **Ian Mongrain**[5,6], **Géraldine Asselin**[5,6], **Sylvie Provost**[5,6], **Marie-Pierre Dubé**[5,6,7], **Eric Nudleman**[4], and **Radha Ayyagari**[4,*]

[1]Mejora Vision MD/Virtual Eye Care MD, Mérida, Yucatán, México

[2]Laboratoire de Diagnostic Moleculaire, Hôpital Maisonneuve Rosemont, Montreal, Quebec, Canada

[3]School of Biotechnology, REVA University, Bengaluru, India

[4]Shiley Eye Institute, University of California San Diego, La Jolla, CA, USA

[5]Montreal Heart Institute, Montreal, Canada

[6]Université de Montréal Beaulieu-Saucier Pharmacogenomics Center, Montreal, Canada

[7]Université de Montréal, Montreal, Canada

[#] These authors contributed equally to this work.

Abstract

Purpose: To investigate the clinical characteristics and genetic basis of inherited retinal degeneration (IRD) in six unrelated pedigrees from Mexico.

Methods: A complete ophthalmic evaluation including measurement of visual acuities, Goldman kinetic or Humphrey dynamic perimetry, Amsler test, fundus photography, and color vision testing was performed. Family history and blood samples were collected from available family members. DNA from members of two pedigrees were examined for known mutations using APEX ARRP genotyping microarray and one pedigree using the APEX LCA genotyping microarray. The remaining three pedigrees were analyzed using a custom designed targeted capture array covering the exons of 233 known retinal degeneration genes. Sequencing was performed on Illumina HiSeq. Reads were mapped against hg19, and variants were annotated using GATK and filtered by exomeSuite. Segregation and ethnicity-matched control sample analyses were performed by dideoxy sequencing.

Results: Six pedigrees with IRD were analyzed. Nine rare or novel, potentially pathogenic variants segregating with the phenotype were detected in *IMPDH1, USH2A, RPE65, ABCA4*, and *FAM161A* genes. Among these, six were known mutations while the remaining three changes in *USH2A, RPE65*, and *FAM161A* genes have not been previously reported to be associated with

[*]Corresponding author, Radha Ayyagari, Ph.D., Shiley Eye Institute, Jacobs Retina Center, Rm 206, University of California San Diego, 9415 Campus Point Drive, San Diego, CA, 92093, rayyagari@ucsd.edu.

IRD. Analysis of 100 ethnicity-matched controls did not detect the presence of these three novel variants indicating, these are rare variants in the Mexican population.

Conclusions: Screening patients diagnosed with IRD from Mexico identified six known mutations and three rare or novel potentially damaging variants in *IMPDH1, USH2A, RPE65, ABCA4* and *FAM161A* genes that segregated with disease.

Introduction:

Inherited retinal dystrophies (IRD) are a group of conditions that cause irreversible vision loss due to degeneration of the retina or retinal pigment epithelium (RPE) (1, 2). These are genetically and phenotypically heterogeneous conditions that show different modes of inheritance (3). Dominantly inherited conditions are more common in the Caucasian population while recessively inherited conditions are more common in populations with higher consanguinity. Mutations in more than 250 genes have been identified in patients with IRD while causative mutations in about 40% to 50% of cases have yet to be determined (4). Some of the genes involved in causing IRD are also associated with syndromic conditions that include RD.

The molecular basis of retinal degeneration in the Mexican population has not been studied extensively. A few studies involving the analysis of IRD in this population revealed mutations in *PRPF31, RDH12, CRB1, RHO*, and *MFRP* (5–12). However, in the Mexican population, approximately 15–20% of RP cases are autosomal dominant, 20–25% are autosomal recessive, 10–15% are X-linked recessive, and 40–55% are considered to have “simplex” inheritance (8). Higher incidence of recessive IRDs has been reported in subpopulations with high consanguinity (13). Inbreeding has been reported in certain regions of southern Mexico including the Yucatan peninsula; IRD in these populations have not been studied extensively.

In this study, we describe the clinical and genetic analysis of seven unrelated pedigrees from the Yucatan peninsula of Mexico and the identification of potential causative mutations segregating with disease in six pedigrees.

METHODS

Patients:

Research procedures were performed in accordance with the Declaration of Helsinki and with the approval of the UC San Diego institutional review board and the Clinical RetMxMap 2006 - institutional review board. Medical and family history and blood samples were collected from affected members and available unaffected relatives. The six pedigrees described in this study are a sub-set of a larger cohort of 25 unrelated IRD families recruited from Mexico and the studies on the remaining 19 pedigrees are underway.

Clinical examination:

Twenty-seven individuals from six pedigrees from Mexico were studied (Figure 1). Ophthalmic evaluation including measurement of best-corrected visual acuity (BCVA),

Goldmann kinetic perimetry and color vision testing were performed as described earlier (14). In pedigree Mex RD105, patient II:1 visual acuity was recorded at “fix and follow” at age 4. Retinal changes were also evaluated by fundus photography, fluorescein angiography and spectral-domain optical coherence tomography (SD-OCT) in selected patients. Medical records of affected members were reviewed.

Genetic Analysis:

DNA was isolated from blood samples. In three pedigrees, exonic regions of 233 IRD genes (Table S1) were captured using selective probes panel designed by our laboratory and sequenced on Illumina HiSeq. Sequence read mapping, variant calling and annotation were performed as described earlier (15, 16). The detected variants were filtered by exomeSuite software to identify rare or novel, potentially pathogenic changes in genes known to be associated with retinal degeneration (17). Patients from three other pedigrees were screened for known mutations associated with retinal degeneration using APEX ARRP (two pedigrees) and LCA (one pedigree) genotyping microarrays (18, 19). Segregation analysis and screening of ethnicity-matched control samples was performed by dideoxy sequencing (20).

RESULTS:

Six pedigrees with IRD were recruited from the Yucatan peninsula of Mexico (Figure 1 A-F). Phenotype evaluation revealed progressive retinal degeneration in affected members of these families (Table 1 & Figure 2 A-J). Genetic analysis identified 9 causative mutations in six of these pedigrees in five different genes (Table 1). Among the pedigrees with mutations in known IRD genes, the phenotype segregated in the autosomal dominant mode in one while the remaining five pedigrees showed autosomal recessive inheritance of IRD.

Mex RD11:

The heterozygous mutation c.676G>A (p.Asp226Asn) observed in *IMPDH1* segregated with dominant IRD in pedigree Mex RD11 (Fig 1A and Fig 2A). This mutation was reported previously in patients with dominant RP (21). The affected male II-2 in pedigree Mex RD11 reported onset of vision abnormalities at age 33. He reported nyctalopia at age 48 with no peripheral vision abnormalities until late in his seventh decade. His distance vision measured 20/60 in the right eye, and 20/80 in the left eye, and near vision of 20/20 in both eyes. Goldmann perimetry remained full 40 degrees horizontal with III isopter with both eyes at age 62. His affected son, III-3, noticed dark adaptation abnormalities by age 33. Another affected son III-4 reported peripheral vision abnormalities at age 10 and was diagnosed with RP. The fundus photographs of these three patients exhibited generalized pigment mottling with mild pigment clumping (representative fundus photograph of one patient, Fig 2A). There was less severe vascular attenuation with atrophic nasal vessels observed in-patient III-3. OCT demonstrated macular cysts in one out of three patients. Patients with *IMPDH1* mutations have been reported with early childhood onset vision loss with visual acuities from 20/200 to 20/400 by age 40, severe retinal changes by fundus examination, and declared legally blind before age 40 (22–24). The retinal changes observed in these patients were extensive with Bull’s eye maculopathy (24). Overall, the phenotype of pedigree Mex

RD11 appears to be less severe compared to the phenotype of patients with *IMPDH1* mutations reported in the literature.

Mex RD1 and Mex RD101:

Mutations in the *USH2A* gene were observed in two pedigrees, Mex RD1 (Fig 1B) and Mex RD101 (Fig 1C), with recessive IRD. Mex RD1 had compound heterozygous mutations; a novel nonsense variant c.10820A>C (p.His3607Pro) and a previously reported mutation c. 11864G>A (p.Trp3955*) (25). A previously reported homozygous *USH2A* mutation c. 2276G>T (p.Cys759Phe) was observed in the Mex RD101 pedigree (Table 1)(26, 27). Neither of the two affected siblings of Mex RD1 (Fig 1B) had sensorineural hearing loss. Patient II:1 (Fig 1B) in this pedigree first noticed constriction of visual fields and nyctalopia at age 23. However, she did not complain of a functional deficit until the late 4th decade of life. At age 41, her best-corrected vision at distance was 20/80 OU and best-corrected vision at near was 20/20. Visual fields were constricted to 15–20 degrees by Humphrey perimeter. No macular cysts were observed by OCT at this age. Fundus evaluation from patients II:1 and II:3, revealed peripheral pigmentary changes, narrowing of retinal vessels and RPE changes in the macula of both eyes (Fig 2B and 2C). Similarly, Patient II:1 in Mex RD101(Fig 1C) reported vision abnormalities since age 68. At age 78, her best-corrected near visual acuity was 20/400 at 15cm OU. Her pupils were 1+ sluggish. Visual fields by confrontation were unreliable. Anterior segment examination was significant for 3+ nuclear sclerosis OU. Fundus evaluation revealed diffuse peripheral clumps of pigment and narrowing of vessels (Fig 2D). The onset of disease in both pedigrees was observed to be quite late (after 4th decade) (Fig 1B and 1C). The *USH2A* mutation p.Cys759Phe was previously reported in patients with nonsyndromic RP. Later this variant was also observed in a few normal individuals thereby casting doubt on the involvement of this variant in causing pathology (28). Patient II-1 of pedigree Mex RD101 had no other damaging variants in the RD genes tested. The phenotype in this patient with no significant vision loss until age 68 years, suggested a less severe phenotype associated with the p.Cys759Phe mutation and may explain the lack of retinal pathology in some of the younger individuals carrying this mutation in the homozygous state.

Mex RD105:

Analysis of Mex RD105 family members (Fig 1D) with a diagnosis of LCA revealed compound heterozygous mutations, c.311G>T (p.Gly104Val) and c.370C>T (p.Arg124*) in the *RPE65* gene. The novel variant p.Gly104Val has not been reported in patients with IRD, while p.Arg124* was observed previously in a patient with retinitis pigmentosa (29). The four year-old affected female II:1 showed healthy appearing optic nerves, macula and retinal vessels (Fig 2E). Her best-corrected near vision was 20/30, 10/10 at 10 cm, OS ET 2PD, hypermetropia of R+4.25, +5.00 cc ET’ 1DD; distance vision was not reliable. Her vision abnormalities started at age one and nystagmus at age two. Her parents reported a habit of frequent sun gazing. By age 7, her vision deteriorated to HM at 10cm.

Mex RD100:

A previously known homozygous mutation c.6306C>A (p.Asp2102Glu) in *ABCA4* was observed in Mex RD100 with two siblings affected with recessive RD and one unaffected

sibling (Fig 1E) (30). The affected male II:2 complained of blurred vision at age 13 with no color vision abnormalities. He was diagnosed with severe myopia of −6.00 and Stargardt's dystrophy at age 17. At age 29 his visual acuity was 20/40, fluorescein angiography and fundus pictures showed hyperfluorescence in the fovea, and macular RPE atrophy and pigmentary clumping surrounded the fovea in both eyes (Fig 2F and 2G). His sister II:3, at age 33, had abnormal color vision and near visual acuities were 20/40 at 24 cm and 20/200 at 16 cm (Table 1). Fundus photography showed diffuse generalized RPE atrophy throughout the fundus with small patches of pigmentary clumping (Fig 2H). No micropsia or metamorphosis was seen and the Amsler test was negative.

Mex RD107:

Compound heterozygous mutations of a previously reported nonsense variant c.1567C>T (p.Arg523*) (31) and a novel nonsense variant c.1759G>T (p.Gly587*) were observed in the *FAM161A* (NM_001201543.2) gene in the Mex RD107 pedigree (Fig 1F). *FAM161A* gene mutations are associated with RP (32). The phenotype observed in all three affected patients was similar (representative fundus images, Fig 2I and 2J). The 13 year-old affected female II:4 of Mex RD107 reported vision abnormalities since age 11 and photophobia since age 13. Red-Green color vision abnormalities were reported since age 16. At this age, her best-corrected visual acuity was 20/50 OU and near vision was 20/20 (Table 1). Fundus evaluation revealed mild atrophic changes in the RPE throughout the fundus in patient II-1 and II-3 (Fig 2I and 2J). The optic nerve had tilted insertion with a crowded appearing optic cup. This phenotype appears similar to that reported by Langmann et al. in patients with *FAM161A* mutations (32). However, no optic disc pallor was observed in any of these patients even at age 40, contrary to what was reported by Bandah-Rozenfeld et al (31). The p.Arg523* mutation observed in this pedigree has been reported previously in RP patients with Syrian, Libyan, and Israeli Jewish ancestry and determined to be a founder mutation in the Israeli Jewish population (31). Haplotype analysis of Mex RD107 may reveal if this variant in the Mexican population is of Jewish origin.

Discussion:

Currently, limited information is available on the genetic basis of inherited retinal degenerations in the Mexican population. Our studies on 6 Mexican pedigrees identified 9 mutations in known IRD genes with three being novel and six being previously reported (5–12). A study of Mexican individuals with autosomal dominant retinitis pigmentosa (RP) demonstrated a mutation frequency in the *RHO* gene of 17%, a lower mutation frequency than the 25–40% seen in other studies (8, 33). In total, we analyzed 25 pedigrees from Mexico for mutations in known RD genes using methods ranging from targeted mutation screening to exome sequencing of 233 known IRD genes. We identified previously reported mutations or potentially pathogenic variants in known RD genes in 6 pedigrees. In one dominant RD pedigree, variants were observed in the *IMPDH1* gene; in five recessive pedigrees, variants were observed in *USH2A, RPE65, ABCA4*, and *FAM161A* genes. A total of 9 causative variants were detected including 3 changes that have not been previously reported to be associated with IRD (Table 1). In the remaining 19 pedigrees, no mutations were detected in genes previously implicated in IRD by selective capture and sequencing of

the coding regions of 233 known RD genes. The mutation detection rate appears to be low in our cohort compared to the identification of mutations in known genes in about 50% to 60% of cases in other populations (4, 34, 35). The lower mutation detection rate could be due to the limitations of the methodologies used. The APEX arrays with known mutations in arRD genes used for this study did not contain all the mutations known to date. Similarly, the targeted exome capture probes are designed to screen only 233 out of the more than 256 genes known today. In addition, mutation screening using selective capture probes can only detect single base changes and small sequence alterations located in exons while additional types of sequence alterations remain undetected (36, 37). These limitations may contribute to the lower mutation detection rate observed in this study. Furthermore, a larger sample size of patients from the Yucatan peninsula may be needed to better determine the proportion of cases with known RD gene mutations.

Although the number of pedigrees analyzed in our study is small, identification of 3 novel potential mutations in six pedigrees and lack of mutations in known genes tested in 19 of the 25 pedigrees may suggest the potential involvement of novel mutations in known RD genes or the involvement of novel genes in causing RD in our patient cohort from the Yucatan peninsula of Mexico. More than 50 indigenous ethnic groups inhabit Mexico and a study examining 20 of these revealed a significant genetic diversity among the groups (38). These ethnic groups were also found to be significantly divergent from people of European ancestry; some of the indigenous populations appear to be isolated. In general, the Mexican population is a complex admixture between Europeans, Amerindians and a minor proportion of other populations. Because of the unique structure of this population, establishing the variants associated with IRD in this population will be valuable in providing more accurate molecular diagnosis and improved care to patients of Mexican origin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: This work was funded, in part, by NIH-EY021237, NIH-P30EY022589, Foundation Fighting Blindness, and Research to Prevent Blindness.

References:

1. Heckenlively JR. Retinitis Pigmentosa. 1 ed Philadelphia: J.B Lippincott Company; 1988 269 p.
2. Fahim AT, Daiger SP, Weleber RG. Retinitis Pigmentosa Overview. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, et al., editors. GeneReviews(R) Seattle (WA)1993.
3. Farber DB, Heckenlively JR, Sparkes RS, Bateman JB. Molecular genetics of retinitis pigmentosa. West J Med. 1991;155(4):388–99. [PubMed: 1771877]
4. Daiger SP, Sullivan LS, Bowne SJ. Genes and mutations causing retinitis pigmentosa. Clin Genet. 2013;84(2):132–41. [PubMed: 23701314]
5. Chacon-Camacho OF, Camarillo-Blancarte L, Zenteno JC. OCT findings in young asymptomatic subjects carrying familial BEST1 gene mutations. Ophthalmic Genet. 2011;32(1):24–30. [PubMed: 21077756]
6. Chacon-Camacho OF, Granillo-Alvarez M, Ayala-Ramirez R, Zenteno JC. ABCA4 mutational spectrum in Mexican patients with Stargardt disease: Identification of 12 novel mutations and

evidence of a founder effect for the common p.A1773V mutation. Exp Eye Res. 2013;109:77–82. [PubMed: 23419329]

7. Chacon-Camacho OF, Jitskii S, Buentello-Volante B, Quevedo-Martinez J, Zenteno JC. Exome sequencing identifies RDH12 compound heterozygous mutations in a family with severe retinitis pigmentosa. Gene. 2013;528(2):178–82. [PubMed: 23900199]
8. Matias-Florentino M, Ayala-Ramirez R, Graue-Wiechers F, Zenteno JC. Molecular screening of rhodopsin and peripherin/RDS genes in Mexican families with autosomal dominant retinitis pigmentosa. Curr Eye Res. 2009;34(12):1050–6. [PubMed: 19958124]
9. Perez-Cano HJ, Garnica-Hayashi RE, Zenteno JC. CHM gene molecular analysis and X-chromosome inactivation pattern determination in two families with choroideremia. Am J Med Genet A. 2009;149A(10):2134–40. [PubMed: 19764077]
10. Rivera-Vega MR, Chinas-Lopez S, Vaca AL, Arenas-Sordo ML, Kofman-Alfaro S, Messina-Baas O, et al. Molecular analysis of the NDP gene in two families with Norrie disease. Acta Ophthalmol Scand. 2005;83(2):210–4. [PubMed: 15799735]
11. Villanueva A, Willer JR, Bryois J, Dermitzakis ET, Katsanis N, Davis EE. Whole exome sequencing of a dominant retinitis pigmentosa family identifies a novel deletion in PRPF31. Invest Ophthalmol Vis Sci. 2014;55(4):2121–9. [PubMed: 24595387]
12. Zenteno JC, Buentello-Volante B, Quiroz-Gonzalez MA, Quiroz-Reyes MA. Compound heterozygosity for a novel and a recurrent MFRP gene mutation in a family with the nanophthalmos-retinitis pigmentosa complex. Mol Vis. 2009;15:1794–8. [PubMed: 19753314]
13. Li L, Chen Y, Jiao X, Jin C, Jiang D, Tanwar M, et al. Homozygosity Mapping and Genetic Analysis of Autosomal Recessive Retinal Dystrophies in 144 Consanguineous Pakistani Families. Invest Ophthalmol Vis Sci. 2017;58(4):2218–38. [PubMed: 28418496]
14. Duncan JL, Roorda A, Navani M, Vishweswaraiah S, Syed R, Soudry S, et al. Identification of a novel mutation in the CDHR1 gene in a family with recessive retinal degeneration. Arch Ophthalmol. 2012;130(10):1301–8. [PubMed: 23044944]
15. DePristo MA, Banks E, Poplin R, Garimella KV, Maguire JR, Hartl C, et al. A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nat Genet. 2011;43(5):491–8. [PubMed: 21478889]
16. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, et al. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res. 2010;20(9):1297–303. [PubMed: 20644199]
17. Maranhao B, Biswas P, Duncan JL, Branham KE, Silva GA, Naeem MA, et al. exomeSuite: Whole exome sequence variant filtering tool for rapid identification of putative disease causing SNVs/indels. Genomics. 2014;103(2–3):169–76. [PubMed: 24603341]
18. Avila-Fernandez A, Cantalapiedra D, Aller E, Vallespin E, Aguirre-Lamban J, Blanco-Kelly F, et al. Mutation analysis of 272 Spanish families affected by autosomal recessive retinitis pigmentosa using a genotyping microarray. Mol Vis. 2010;16:2550–8. [PubMed: 21151602]
19. Zernant J, Kulm M, Dharmaraj S, den Hollander AI, Perrault I, Preising MN, et al. Genotyping microarray (disease chip) for Leber congenital amaurosis: detection of modifier alleles. Invest Ophthalmol Vis Sci. 2005;46(9):3052–9. [PubMed: 16123401]
20. Cukras C, Gaasterland T, Lee P, Gudiseva HV, Chavali VR, Pullakhandam R, et al. Exome analysis identified a novel mutation in the RBP4 gene in a consanguineous pedigree with retinal dystrophy and developmental abnormalities. PloS one. 2012;7(11):e50205. [PubMed: 23189188]
21. Bowne SJ, Sullivan LS, Blanton SH, Cepko CL, Blackshaw S, Birch DG, et al. Mutations in the inosine monophosphate dehydrogenase 1 gene (IMPDH1) cause the RP10 form of autosomal dominant retinitis pigmentosa. Hum Mol Genet. 2002;11(5):559–68. [PubMed: 11875050]
22. Jordan SA, Farrar GJ, Kenna P, Humphries MM, Sheils DM, Kumar-Singh R, et al. Localization of an autosomal dominant retinitis pigmentosa gene to chromosome 7q. Nat Genet. 1993;4(1):54–8. [PubMed: 8513324]
23. Kozma P, Hughbanks-Wheaton DK, Locke KG, Fish GE, Gire AI, Spellicy CJ, et al. Phenotypic characterization of a large family with RP10 autosomal-dominant retinitis pigmentosa: an Asp226Asn mutation in the IMPDH1 gene. Am J Ophthalmol. 2005;140(5):858–67. [PubMed: 16214101]

24. Coussa RG, Chakarova C, Ajlan R, Taha M, Kavalec C, Gomolin J, et al. Genotype and Phenotype Studies in Autosomal Dominant Retinitis Pigmentosa (adRP) of the French Canadian Founder Population. Invest Ophthalmol Vis Sci. 2015;56(13):8297–305. [PubMed: 26720483]
25. van Wijk E, Pennings RJ, te Brinke H, Claassen A, Yntema HG, Hoefsloot LH, et al. Identification of 51 novel exons of the Usher syndrome type 2A (USH2A) gene that encode multiple conserved functional domains and that are mutated in patients with Usher syndrome type II. Am J Hum Genet. 2004;74(4):738–44. [PubMed: 15015129]
26. Lenassi E, Vincent A, Li Z, Saihan Z, Coffey AJ, Steele-Stallard HB, et al. A detailed clinical and molecular survey of subjects with nonsyndromic USH2A retinopathy reveals an allelic hierarchy of disease-causing variants. Eur J Hum Genet. 2015.
27. Blanco-Kelly F, Jaijo T, Aller E, Avila-Fernandez A, Lopez-Molina MI, Gimenez A, et al. Clinical aspects of Usher syndrome and the USH2A gene in a cohort of 433 patients. JAMA ophthalmology. 2015;133(2):157–64. [PubMed: 25375654]
28. Rivolta C, Sweklo EA, Berson EL, Dryja TP. Missense mutation in the USH2A gene: association with recessive retinitis pigmentosa without hearing loss. Am J Hum Genet. 2000;66(6):1975–8. [PubMed: 10775529]
29. Morimura H, Fishman GA, Grover SA, Fulton AB, Berson EL, Dryja TP. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or leber congenital amaurosis. Proc Natl Acad Sci U S A. 1998;95(6):3088–93. [PubMed: 9501220]
30. Zernant J, Schubert C, Im KM, Burke T, Brown CM, Fishman GA, et al. Analysis of the ABCA4 gene by next-generation sequencing. Invest Ophthalmol Vis Sci. 2011;52(11):8479–87. [PubMed: 21911583]
31. Bandah-Rozenfeld D, Mizrahi-Meissonnier L, Farhy C, Obolensky A, Chowers I, Pe'er J, et al. Homozygosity mapping reveals null mutations in FAM161A as a cause of autosomal-recessive retinitis pigmentosa. Am J Hum Genet. 2010;87(3):382–91. [PubMed: 20705279]
32. Langmann T, Di Gioia SA, Rau I, Stohr H, Maksimovic NS, Corbo JC, et al. Nonsense mutations in FAM161A cause RP28-associated recessive retinitis pigmentosa. Am J Hum Genet. 2010;87(3): 376–81. [PubMed: 20705278]
33. Corton M, Nishiguchi KM, Avila-Fernandez A, Nikopoulos K, Riveiro-Alvarez R, Tatu SD, et al. Exome sequencing of index patients with retinal dystrophies as a tool for molecular diagnosis. PloS one. 2013;8(6):e65574. [PubMed: 23940504]
34. Huang XF, Huang F, Wu KC, Wu J, Chen J, Pang CP, et al. Genotype-phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy revealed by next-generation sequencing. Genet Med. 2015;17(4):271–8. [PubMed: 25356976]
35. Oishi M, Oishi A, Gotoh N, Ogino K, Higasa K, Iida K, et al. Next-generation sequencing-based comprehensive molecular analysis of 43 Japanese patients with cone and cone-rod dystrophies. Mol Vis. 2016;22:150–60. [PubMed: 26957898]
36. Bujakowska KM, Fernandez-Godino R, Place E, Consugar M, Navarro-Gomez D, White J, et al. Copy-number variation is an important contributor to the genetic causality of inherited retinal degenerations. Genet Med. 2016.
37. Liu MM, Chan CC, Tuo J. Genetic mechanisms and age-related macular degeneration: common variants, rare variants, copy number variations, epigenetics, and mitochondrial genetics. Hum Genomics. 2012;6:13. [PubMed: 23244519]
38. Moreno-Estrada A, Gignoux CR, Fernandez-Lopez JC, Zakharia F, Sikora M, Contreras AV, et al. Human genetics. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science. 2014;344(6189):1280–5. [PubMed: 24926019]

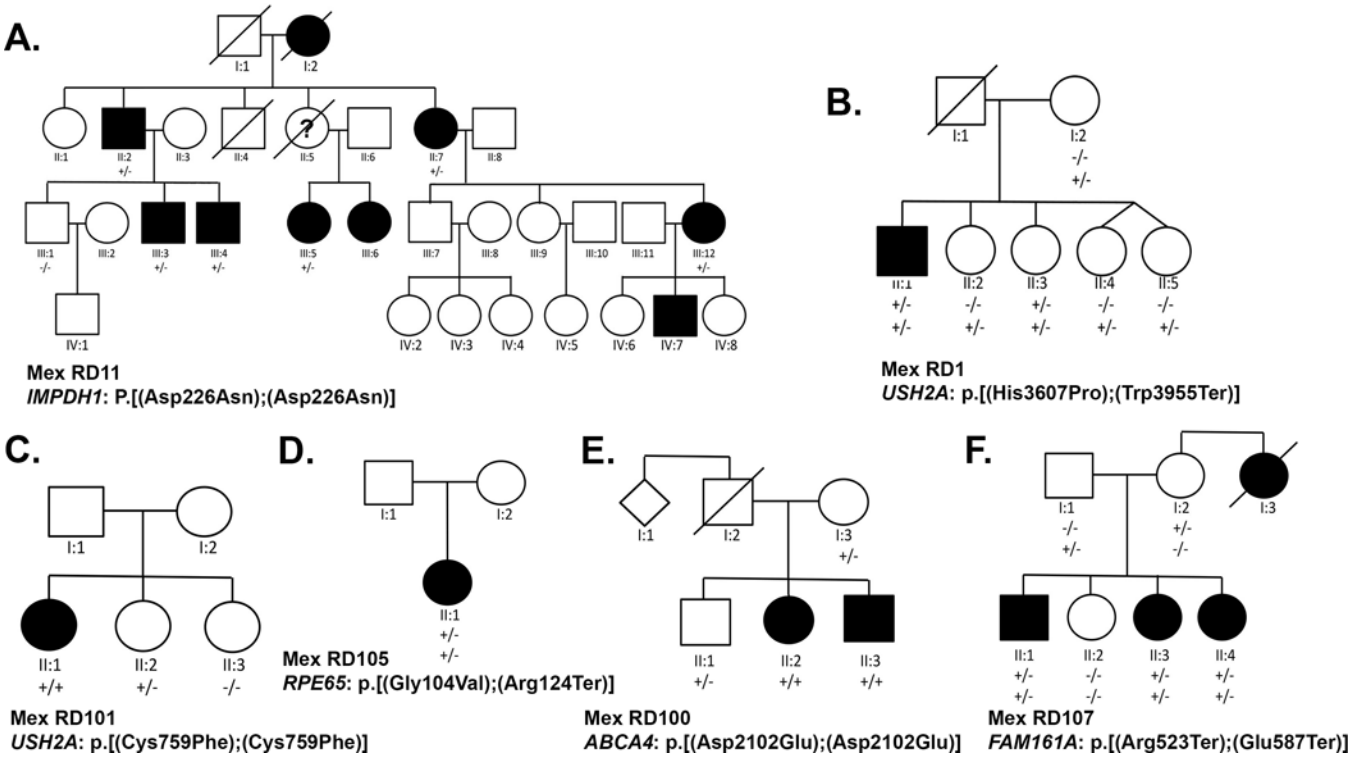

Figure 1:

Mexican RD pedigrees showing segregation of detected mutations. Pedigree numbers and the causative mutations are listed below each pedigree.

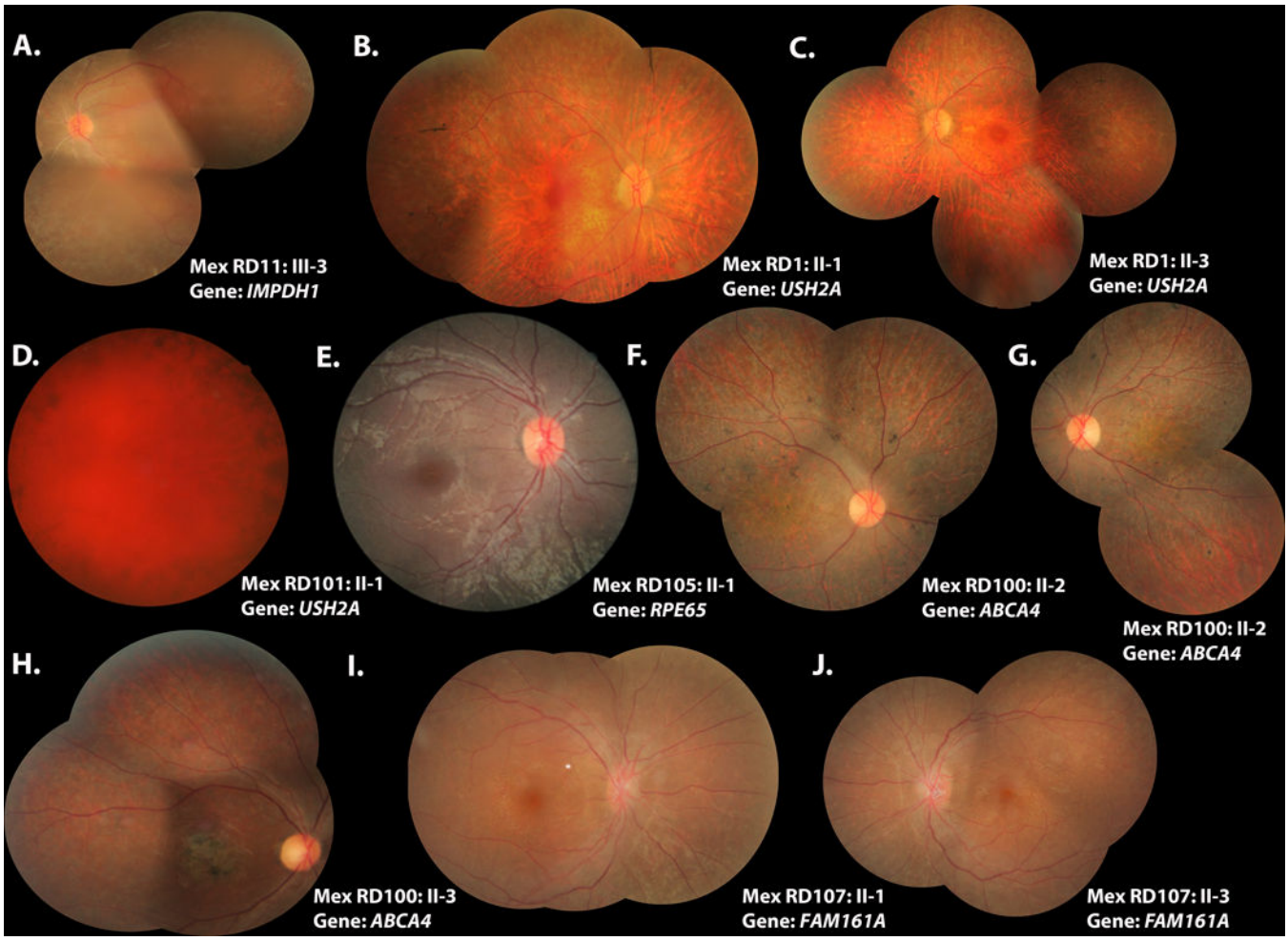

Figure 2:

Fundus photos and OCT images of patients from the Mexican pedigrees described in Figure 1. Patient and pedigree IDs are given at the right bottom corner of each image.

Table 1:

Phenotype and genotype of Mexican pedigrees examined in this study.

Mex RD family	Patient	Age of onset[#]	Age of testing	Visual acuity	Fundus appearance	Gene	cDNA Change (rsID)	Amino acid Change (ExAC freq)	Zygosity	Known to be associated with RD	Analysis Method
11	II-2	33	62	20/60 OD 20/80 OS	Diffuse peripheral pigment clumping	*IMPDH1*	c.676 G>A rs121912550	p.Asp226Asn 0.000008	Het	Yes	APEX adRP array
	III-3	33	33	20/20 OU	Diffuse peripheral pigment clumping, nasal silver vessels						
	III-4	10	31	20/20	Same as III-3						
1	II:1	23	41	20/80 OU	Diffuse peripheral pigment clumping, arterial narrowing. No Pallor of optic nerve	*USH2A*	c.10820A>C rs750321557	p.His3607Pro 0.00005	Het	No	Selective Capture
	II:3	40	40	20/40 OS	Similar to II-1		c.11864G>A rs111033364	p.Trp3955* 0.0001	Het	Yes	
101	II:1	68	78	20/400 OU	Peripheral pigment clumping	*USH2A*	c.2276G>T rs80338902	p.Cys759Phe 0.0008	Hom	Yes	APEX adRP array
105	II:1	1[##]	4	Fixes and follows	Normal fundus appearance	*RPE65*	c.311G>T rs61752875	p.Gly104Val Not available	Het	No	APEX LCA array
				HM by age 7			c.370C>T rs61752877	p.Arg124* 0.00004	Het	Yes	
100	II:2	13	29	20/40 OD	Diffuse generalized RPE atrophy with pigmentary clumping	*ABCA4*	c.6306C>A rs568627877	p.Asp2102Glu 0.00005	Hom	Yes	Selective Capture
	II:3	15	33	20/40 OD 20/200 OS	Diffuse RPE atrophy with macula atrophy						
107	II:4	11	16	20/50 OU	Mild RPE atrophy, peripheral pigment changes	*FAM161A*	c.1567C>T rs202193201	p.Arg523* 0.0002	Het	Yes	Selective Capture
							c.1759G>T Not available	p.Gly587* Not available	Het	No	

[#]Age at which first symptoms are reported by patients or their parents.

[##]105-II:1 age of onset is since birth (near first month mom recall she has abnormal eye movements)