Original Article

Clinical Features of Autosomal Dominant Retinitis Pigmentosa Associated with a Rhodopsin Mutation

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Abstract

Introduction: Retinitis pigmentosa (RP) describes a group of inherited disorders characterised by progressive retinal dysfunction, cell loss and atrophy of retinal tissue. RP demonstrates considerable clinical and genetic heterogeneity, with wide variations in disease severity, progression, and gene involvement. We studied a large family with RP to determine the pattern of inheritance and identify the disease-causing mutation, and then to describe the phenotypic presentation of this family. Materials and Methods: Ophthalmic examination was performed on 46 family members to identify affected individuals and to characterise the disease phenotype. Family pedigree was obtained. Some family members also had fundus photographs, fluorescein angiography, and/or optical coherence tomography (OCT) analysis performed. Genetic linkage was performed using short tandem repeat (STR) polymorphic markers encompassing the known loci for autosomal dominant RP. Finally, DNA sequencing was performed to identify the mutation present in this family. Results: Clinical features included nyctalopia, constriction of visual fields and eventual loss of central vision. Sequence analysis revealed a G-to-T nucleotide change in the Rhodopsin gene, predicting a Gly-51-Val substitution. Conclusions: This large multi-generation family demonstrates the phenotypic variability of a previously identified autosomal dominant mutation of the Rhodopsin gene.

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Key words: Hereditary eye diseases, Retinal degeneration, Retinopathy, Rod cone dystrophies

Introduction

Retinitis pigmentosa (RP) is the most prevalent group of inherited retinopathies. This spectrum of diseases affects approximately 1 in 4800 individuals.[1] The disease has both highly variable clinical and genetic heterogeneity. Variations exist in the severity of disease, age of onset, rate of progression and clinical findings. Patients initially experience nyctalopia (night blindness), which then progresses to restriction of peripheral vision and eventual loss of central vision. Clinical findings include bone spicule degeneration, attenuation of retinal vessels, waxy optic nerve pallor and loss of retinal pigment epithelium (RPE). Patients often develop posterior subcapsular cataracts, as well as cystoid macular oedema. On histopathologic evaluation, patients initially suffer from loss of rod photoreceptors, which then progresses to loss of cone photoreceptor cells. On electrophysiologic testing, patients with advanced disease will have diminished or non-detectable electroretinograms. At this time, there is no effective treatment for RP.

RP is inherited in several patterns of inheritance. Forty-three per cent of patients are found to have autosomal dominant transmission. In 20% of cases, the trait is autosomal recessive. X-linked RP comprises approximately 8% of patients. Sporadic cases account for 23% of cases. In 6% of cases, the inheritance is unknown.[1]

Autosomal dominant RP is associated with a variety of known mutations in gene coding for the photoreceptors and the RPE. Currently, 13 autosomal dominant genes have been identified, and 12 of these have had their gene product thoroughly described. These are: RP18/HPRP3(1q),[2] RP4(RHO)/Rhodopsin(3q),[3] RP7(RDS)/ RDS (Peripherin)

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(6p),[4,5] RP9/PIM1K (7p),[6] RP10/IMPDH1 (7q),[7,8] RP1/RP1 (8q),[9,10] ROM1/ROM1 (11q),[11] RP27(NRL)/NRL (14q),[12] RP13/PRPF8 (17p),[13] RP17/CA4 (17q),[14,15] FSCN2/ Retinal fascin (17q),[16] RP11/PRPF31 (19q)[17] and CRX(19q).[18] These genes' various functions include roles in phototransduction, structure of the photoreceptors, the retinoid cycle and RNA splicing. One example is the RHO locus (3q) which encodes the photoreceptor molecule Rhodopsin; this is a major disease gene in autosomal dominant RP. We investigated 46 members of a large, Caucasian, Utah family with RP to determine the pattern of inheritance and identify the disease-causing mutation.

Materials and Methods

Approval for this study was obtained from the Institutional Review Board of the University of Utah, USA, and informed consent was obtained from all participants in accordance with the tenets of the Declaration of Helsinki and guidelines of the National Institute of Health (NIH) on human subject research. A complete ophthalmic history and examination

Table 1. Characteristics of Affected Individuals

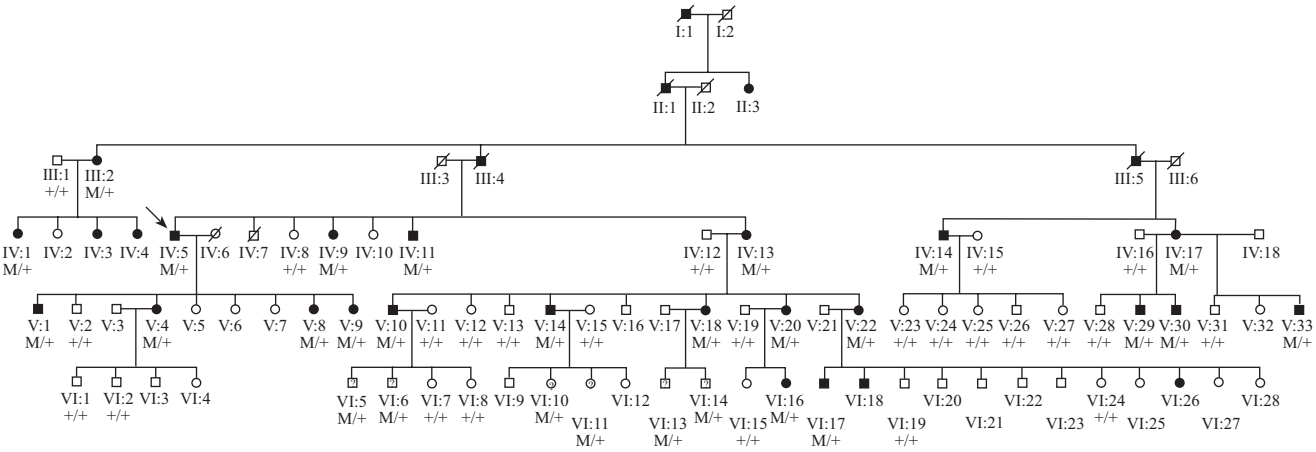
Patient No.	Age/Sex	Age of onset	BCVA OD	BCVA OS	Nyctalopia	Constricted visual fields	Bone spicule pigmentation	CME	Other findings
IV:5	55/M	25	20/25	20/40	Yes	Yes	OU	Mild, OU	Early nuclear cataract OD, PCIOL OS, OCT – mild macular thickening
III:2	86/F	29	HM 1'	HM 1'	Yes	Yes	OU	Yes	Nuclear cataracts OU
IV:1	68/F	30	20/40	20/400	Yes	No	OU	No	Optic nerve pallor
IV:9	74/F	–	20/40	20/30	–	–	OU	No	
IV:11	68/M	–	20/25	20/25	Yes	Yes	OU	No	
IV:13	80/F	30	–	–	Yes	–	OU	No	
IV:14	59/M	–	20/50	20/70	Yes	Yes	OU	No	
IV:17	66/F	25	–	–	Yes	Yes	OU	No	Legally blind at age 14
V:1	26/M	21	20/20	20/20	Yes	–	OU	No	
V:4	33/F	–	–	–	–	–	–	No	
V:8	21/F	12	20/40	20/40	Yes	Yes	OU	Yes	OCT – increased macular thickness OU
V:9	16/F	–	20/30	20/25	Yes	Yes	OU	Mild, OU	OCT – increased macular thickness OD>OS
V:10	36/M	15	20/20	20/20	Yes	No	OU	No	Peripapillary atrophy
V:14	47/M	–	20/20	20/20	Yes	No	OU	No	
V:18	40/F	–	20/20	20/20	Yes	No	OU	No	
V:20	57/F	16	20/40	20/30	Yes	Yes	OU	No	
V:22	60/F	40	20/30	20/40	Yes	Yes	OU	No	
V:29	34/M	–	20/20	20/20	No	Yes	No	No	
V:30	29/M	15	–	–	Yes	Yes	OU	No	
V:33	42/M	13	–	–	Yes	Yes	OU	No	Ring degeneration OU
VI:5	16/M	AS	20/20	20/20	No	No	No	No	
VI:6	10/M	AS	20/20	20/20	No	No	No	No	
VI:10	15/F	AS	20/20	20/20	No	No	No	No	
VI:11	18/F	AS	20/20	20/20	No	No	No	No	
VI:13	22/M	AS	20/20	20/20	No	No	OU	No	
VI:14	20/M	AS	20/20	20/20	No	No	No	No	
VI:17	30/M	8	20/20	CF 5'	Yes	Yes	OU	No	Unknown why BCVA OS<<OD

AS: asymptomatic; BCVA: best corrected visual acuity at time of examination; CF: counting fingers at specified distance in English feet; CME: cystoid macular oedema; HM: hand movements; OCT: optical coherence tomography; OD: right eye; OS: left eye; OU: both eyes; PCIOL: post-cataract intra-ocular lens

Patient number refers to designation on pedigree (Fig. 1).

All ages are expressed in years.

A dash (–) signifies data is not available.



Squares indicate males	Symbols with question mark, patients too young to manifest disease phenotype
Circles, females	Symbol with arrow, proband
Slashed symbols, deceased	Roman numerals indicate generation number
Solid symbols, affected	Arabic numerals indicate individual number within the generation
Open symbols, unaffected	Mutant allele is indicated by "M"; normal allele by "+"

Fig. 1. Pedigree of family with autosomal dominant retinitis pigmentosa.

was performed on 46 individuals in the family and included assessment of visual acuity and detailed examination of the anterior segment and fundus using colour photography. Each individual donated a blood sample for DNA extraction and analysis. Seven spouses of affected individuals also donated blood to serve as normal controls. Several affected individuals also underwent fluorescein angiography and/or optical coherence tomographic (OCT) assessment. Individuals were diagnosed with RP if they had nyctalopia and/or decreased visual fields in combination with bone spicule pigmentation on fundus examination.

Initial genetic linkage studies were performed on all living affected patients whose disease status could be determined with certainty. Genomic DNA was extracted from blood samples by standard methods.[15] Genetic linkage analysis was performed using short tandem repeat (STR) polymorphic markers encompassing the known loci for adRP including: D1S252, D1S498 (RP18/HPRP3); D3S2460, D3S1764 (RP4/RHO); D6S2410, D6S1017 (RP7/RDS); D7S435, D7S628, D7S2515 (RP9/PIM1K); D7S3061, D7S1804 (RP10/IMPDH1); D8S1110, D8S1464 (RP1); D17S849, D17S831, (RP13/PRPF8); D17S1606, D17S701 (RP17/CA4); D19S559, D19S589, D19S254 (RP11/PRPF31). Linkage analysis was then used to determine the LOD score in each locus using the LINKAGE software package (Version 5.1).[19-21] Mutation screening was performed by direct sequencing of PCR-amplified genomic DNA corresponding to each exon of the RHO locus for each of the affected individuals as described previously.[15] Once the mutation was identified, screening for the mutation was performed on asymptomatic members of the family.

Results

A 6-generation pedigree was studied and revealed autosomal dominant inheritance (Fig. 1). Ophthalmic examination found 21 affected individuals among the 46 tested family members. Age of onset was from 8 to 40 years and visual acuity ranged from 20/20 in children to hand motion in older adults (Table 1). Fundus examination and fluorescein angiography in affected patients demonstrated a typical clinical phenotype of RP including bone spicule pigmentation in the peripheral retina and extensive retinal and RPE atrophy in the advanced stages of the disease. Optic nerve pallor was observed in 1 patient with advanced disease. Several OCT analyses showed cystoid macular oedema (Figs. 2 to 6)

Sequence analysis revealed a G-to-T nucleotide change at position 152 in the Rhodopsin gene, predicting a Gly-51-Val substitution (Fig. 7) All affected individuals were found to have the mutation. Five younger individuals in the family who were too young to manifest the RP phenotype were also found to have the disease-causing mutation.

Discussion

We studied a large family with autosomal dominant RP. This family harbors a Gly-51-Val substitution mutation that was first described in 1991. This amino acid position corresponds to the first transmembrane domain of the Rhodopsin protein.[22] This mutation causes misfolding of the protein.[23] It is currently unknown how this misfolding leads to the RP phenotype.

Clinically, this family demonstrates dominant inheritance and a large degree of variable expressivity. All individuals in generations III, IV, and V who carry the mutation are

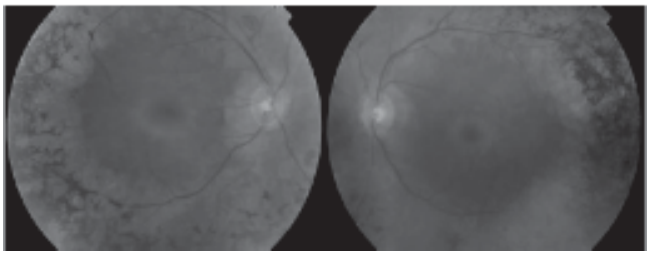


Fig. 2A.

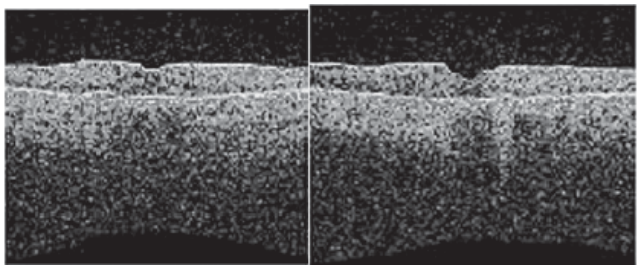


Fig. 2B.

Fig. 2. Patient IV:5, proband A: Fundus photographs of the right and left eyes; this patient had 20/25 OD and 20/40 OS at time of examination; findings include characteristic bone spicule degeneration in the periphery OU, as well as attenuation of vessels. B. OCT examination shows central foveal thickness of 233 µm OD and 189 µm OS; there are no cysts present.

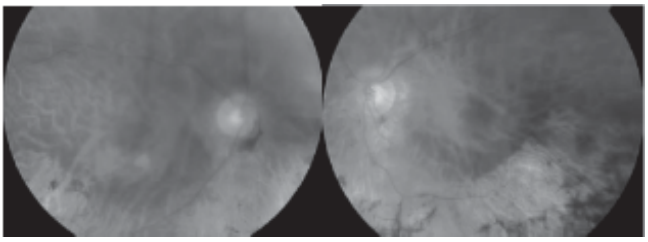


Fig. 3. Patient IV:9 This patient had visual acuity measurement of 20/40 OD and 20/30 OS at time of examination; on fundus examination, there is slight obscuration of view in the right eye due to cataract formation; nevertheless, depigmentation with bone spicule formation in the periphery as well as retinal vascular attenuation are observed OU.

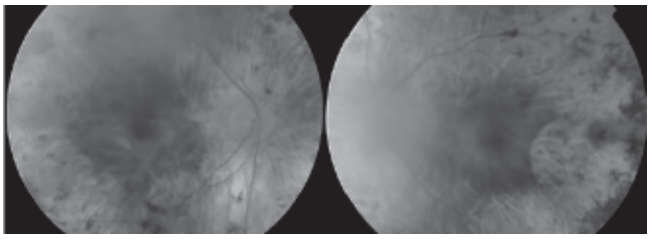


Fig. 4. Patient IV:11 Visual acuity was 20/25 OU at time of examination; on fundus examination, there has been extensive peripheral retinal degeneration as well as vascular attenuation OU.

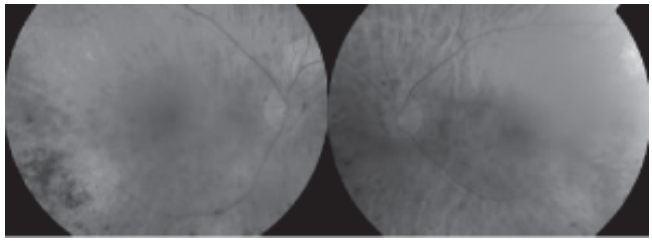


Fig. 5. Individual IV:14 Patient's visual acuity was 20/50 OD and 20/70 OS at time of examination; fundus photographs of the right and left eyes show peripheral retinal degeneration with pigment changes OU.

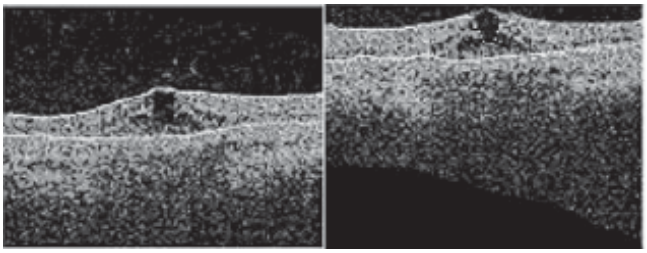


Fig. 6. Patient V:8 OCT. central foveal thickness measurements were 368 µm OD and 344 µm OS; in this patient, there is cyst formation present in each macula.

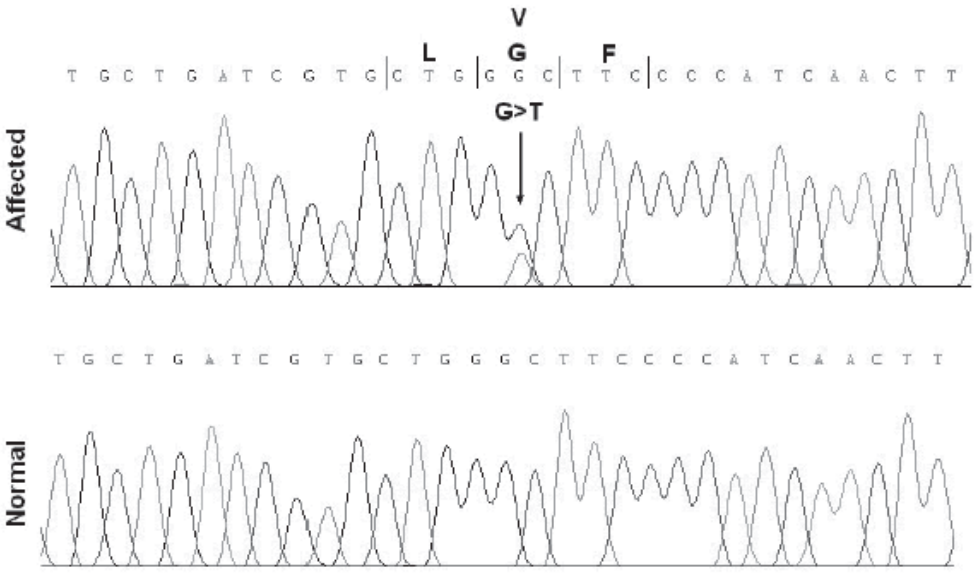


Fig. 7. Direct sequencing analysis of the Rhodopsin gene in affected individuals identified a G-to-T nucleotide change at position 152, predicting a gly-51-Val substitution.

affected, and those 5 individuals in generation VI who were too young at the time of this study to manifest the phenotype can be expected to do so eventually. While all of the affected individuals demonstrate nyctalopia and/or bilateral constriction of visual fields combined with bilateral bone spicule pigmentation on fundoscopic examination, there is wide variation in terms of age of onset and degree of vision loss. Individual V:8, for example, began to have nyctalopia at age 12, while individual V:22 did not have symptoms until age 40. These individuals are first cousins. In terms of variability of vision loss, individual IV:17 was legally blind at age 14, while individual IV:11 has 20/25 vision OU at age 68. These individuals are also first cousins.

Providers caring for RP patients and their families should be aware that even though there is currently no treatment for any form of RP, the highly variable expressivity of the disease means that disease severity and time course of progression cannot be predicted based on other family members. Identification of underlying mutations and subsequent functional studies in autosomal dominant retinitis pigmentosa may provide new insights into pathogenic mechanisms and lead to new avenues of therapeutic intervention.

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