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Mutation spectrum and frequency of the RHO gene in 248 Chinese families with retinitis pigmentosa

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ABSTRACT

Mutations in the rhodopsin gene (RHO) are suggested to be the most common cause of autosomal dominant retinitis pigmentosa (RP). However, the exact spectrum and frequency of RHO mutations in different forms of RP has not been well defined, especially in Chinese populations. In this study, direct cycle sequencing was used to analyze all five coding exons and adjacent intronic regions of RHO in 248 Chinese probands with different forms of non X-linked RP. Eight heterozygous nucleotide changes were detected, including two novel mutations (c.628G>T, p.Val210Phe; c.945C>G, p.Asn315Lys) and six known mutations (c.527C>T, p.Ser176Phe; c.568G>T, p.Asp190Tyr; c.768_770delCAT, p.Ile256del; c.1040C>T, p.Pro347Leu; c.310G>A, p.Val104Ile; c.895G>T, p.Ala299Ser), in 14 probands (nine isolated cases, three from autosomal dominant families, and three from autosomal recessive families). Of the eight mutations, seven were missense changes and one was a small deletion. Six may be pathogenic mutations, and two others (c.310G>A, c.895G>T) may not be causative on their own. The p.Ala299Ser change was present in six of the 248 probands with RP but only in one of 384 normal controls, while the p.Val104Ile was present in two probands but none of the 384 controls. Our results demonstrate an overview of the spectrum and frequency of RP RHO mutations in a Chinese population and emphasize that RHO mutations in isolated RP are not uncommon.

1. Introduction

Retinitis pigmentosa (RP, MIM 268000) is a common form of progressive hereditary retinal degeneration and one of the leading causes of irreversible blindness [1]. The early stage predominantly involves rod photoreceptors and subsequently affects cones. RP is genetically heterogeneous and can be inherited as an autosomal dominant (adRP), autosomal recessive (arRP), X-linked recessive (xlRP), mitochondrial, or digenic trait, of which autosomal recessive is the most frequent form [2,3]. Approximately 10–19% of RP kindreds are autosomal dominant and 6–8% are X-linked recessive; the remaining kindreds are most likely to be autosomal recessive (including most isolated cases) [2,4,5]. RP can present alone (non-syndromic form) or associated with other ocular or systemic abnormalities (syndromic form). At least 53 causative loci or genes have been identified for nonsyndromic RP (RetNet: http://www.sph.uth.tmc.edu/Retnet/sum-dis.htm). Mutations in all of these genes are estimated to be responsible for more than half of RP patients. However, mutations in each of these genes usually account for a few percentages of RP patients with the exception of some genes such as the rhodopsin gene (RHO, MIM 180380).

RHO encodes rhodopsin, a visual pigment that mediates vision in dim light through its interaction with 11-cis-retinal in retinal rod photoreceptors. RHO is the first gene identified to be responsible for RP when mutated [6]. Mutations in RHO are a common cause of adRP [1,6–9], but in rare cases, RHO mutations are associated with arRP [10,11] and autosomal dominant congenital stationary night blindness [12,13]. Although a number of mutations in RHO have been identified, however, the exact spectrum and frequency of RHO mutations in a population with RP has not been well defined due to the following factors: (1) RHO mutational screening was mostly based on indirect sequence analysis, which is known to detect only a portion of mutations, such as single strand conformational analysis (SSCP) or denaturing high performance liquid chromatography (dHPLC), etc.; (2) RHO mutations in singleton/sporadic cases or autosomal recessive RP have not been evaluated well because previous studies on RHO were limited to patients with autosomal dominant RP; and (3) only parts of the five coding exons were screened by sequencing. Thus far, direct sequencing of all five coding exons of RHO has not been reported in an unselected RP population regardless of pattern of inheritance.

In this study, cycle sequencing was used to analyze each of the five coding exons and adjacent intronic regions of RHO in 248 Chinese probands with RP. Included patients came from families

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Table 1
RP families used in this study.

Inheritance	Number of families	Probands	
		Male	Female
Autosomal dominant	37	22	15
Autosomal recessive	25	11	14
Unknown	22	18	4
Sporadic	164	107	57
X-linked (XL)	20	20	0
Total with XL	268	179	90
Total without XL	248	158	90

with adRP, arRP, unknown patterns of inheritance, and cases without a family history (isolated). Our results revealed the spectrum and frequency of the RHO mutation in Chinese patients with RP.

2. Methods

2.1. Patient samples

Patients with RP were collected from our Pediatric and Genetic Clinic, Zhongshan Ophthalmic Center between 1995 and 2009. A total of 268 probands with RP were collected during this period. Twenty of the 268 were excluded from the study because they were from families with xlRP. The remaining 248 probands participating in the study were from families with adRP (37 probands), arRP (25 probands), unknown patterns of inheritance (22 probands), or isolated cases without a family history (164 probands) (Table 1). Recording of the clinical data and preparation of the genomic DNA were performed in the Laboratory of Ophthalmic Genetics & Molecular Biology, Zhongshan Ophthalmic Center as part of our 863-project to identify genes responsible for genetic eye diseases. This study was approved by the IRB of the Zhongshan Ophthalmic Center and followed the tenets of the Declaration of Helsinki and the Guidance of Sample Collection of Human Genetic Diseases (863-Plan) by the Ministry of Public Health of China. Informed consent was obtained from the participating individuals or their guardians prior to the collection of clinical data and genomic samples. A diagnosis of RP was made by senior ophthalmologists (Profs. Zhang and Guo) based on criteria that we have described previously [14]. Genomic DNA was prepared from venous leukocytes in a method described previously [15].

2.2. Mutation detection in RHO

Five pairs of primers (Table 2) were designed and synthesized in order to amplify each of the five coding exons and their adjacent intronic regions of RHO (NCBI human genome build 36.3, NC_000003.11 region: 129247482.129254187 for genomic DNA, NM_000539.3 for mRNA, and NP_000530.1 for protein). DNA fragments encompassing individual exon were amplified by polymerase chain reaction (PCR). The amplicons were analyzed with the ABI BigDye Terminator cycle sequencing kit version 3.1 (Applied Biosystems, Foster City, CA) using an ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Sequencing results from patients and RHO consensus sequences from the NCBI Human Genome Database (NCBI human genome build 36.3, NC_000003.11 region: 129247482.129254187) were imported into the SeqManII program of the Lasergene package (DNAStar Inc., Madison, WI) and then aligned to identify variations. Each variation was initially confirmed by bidirectional sequencing and then evaluated in at least 96 controls. Mutation description followed the recommendation of the Human Genomic Variation Society (HGVS, http://www.hgvs.org/). The possible functional effect of an amino acid substitution due to a mutation was predicted using the Polymorphism Phenotyping v2 (PolyPhen-2) online tool (http://genetics.bwh.harvard.edu/pph2/index.shtml).

2.3. Heteroduplex-single strand conformation polymorphism analysis

Any variation detected in RHO exons 2–5 was further evaluated in 96–384 normal controls by heteroduplex-single strand conformation polymorphism (Heteroduplex-SSCP) analysis as previously described [16]. Samples with aberrant band variations were confirmed by cycle sequencing as described above. The variation in exon 1 of RHO was evaluated in 384 normal controls by cycle sequencing.

3. Results

Eight heterozygous mutations in RHO were detected in 14 of the 248 probands and demonstrated an overall allele mutation frequency of 5.65% (14/248) upon complete sequencing analysis of RHO coding and adjacent regions (Table 3, Fig. 1). The mutation frequencies were 8.11% (3/37) for adRP, 8.00% (2/25) for arRP, 5.49% (9/164) for isolated RP, and none for RP with unknown patterns of inheritance.

Of the eight mutations, one was a deletion and seven were missense. Two were novel [c.628G>T (p.Val210Phe), c.945C>G (p.Asn315Lys)] and six were known mutations [c.527C>T (p.Ser176Phe), c.568G>T (p.Asp190Tyr), c.768_770delCAT (p.Ile256del), c.1040C>T (p.Pro347Leu), c.310G>A (p.Val104Ile), and c.895G>T (p.Ala299Ser)] (Table 3) [17–22]. The c.628G>T and c.945C>G novel mutations involved codons that encoded residues that are comparatively conserved (Fig. 2). Six of the eight mutations were potentially pathogenic but the role of the other two, the c.310G>A and c.895G>T, may not be causative alone based on previous reports by other researchers [21,22]. Of the two possibly benign changes, the c.310G>A (p.Val104Ile) was found in two of the 248

Table 2
Sequences of primers used to amplify the coding region of RHO.

Primer name	Primer sequence (5′–3′)	Size of amplicons	Annealing temperature (°C)
Exon 1-F	5′-CCAGCTGGAGCCCTGAGTGG-3′	627	68
Exon 1-R	5′-AGCAGCCCGGCTATCACCAT-3′		
Exon 2-F	5′-AAATCCCTCTCCCACTCCTG-3′	434	64
Exon 2-R	5′-TTCTGCCCTACACCCCTACC-3′		
Exon 34aF	5′-CCAGGGAGGGAATGTGAAGC-3′	541	66
Exon 34aR	5′-CCGAAGTTGGAGCCCTGGTG-3′		
Exon 34bF	5′-CATCTGCGGCTCCTGCTC-3′	430	66
Exon 34bR	5′-GACTGCTGACCCAAGACTGC-3′		
Exon 5-F	5′-GGGGCGCTGGAATCGTGAG-3′	351	64
Exon 5-R	5′-GGAGCCTATGTGACTTCGTT-3′		

Table 3
Sequence variation detected in RHO of patients and controls.

Variation	Effect	PolyPhen-2 prediction	Frequency in patients	Frequency in controls	Note	References
Pathogenic						
c.527C>T	p.Ser176Phe	Probably damaging	1/248	0/96	Reported	[17]
c.568G>T	p.Asp190Tyr	Probably damaging	1/248	0/96	Reported	[18]
c.628G>T	p.Val210Phe	Probably damaging	1/248	0/96	Novel	
c.768_770delCAT	p.Ile256del		1/248	0/96	Reported	[19]
c.945C>G	p.Asn315Lys	Possibly damaging	1/248	0/96	Novel	
c.1040C>T	p.Pro347Leu	Possibly damaging	1/248	0/96	Reported	[20]
Possibly benign						
c.310G>A	p.Val104Ile	Benign	2/248	0/384	Reported	[21]
c.895G>T	p.Ala299Ser	Benign	6/248*	1/384	Reported	[22]

* $p = 0.032$ (frequency in patients compared with that in controls).

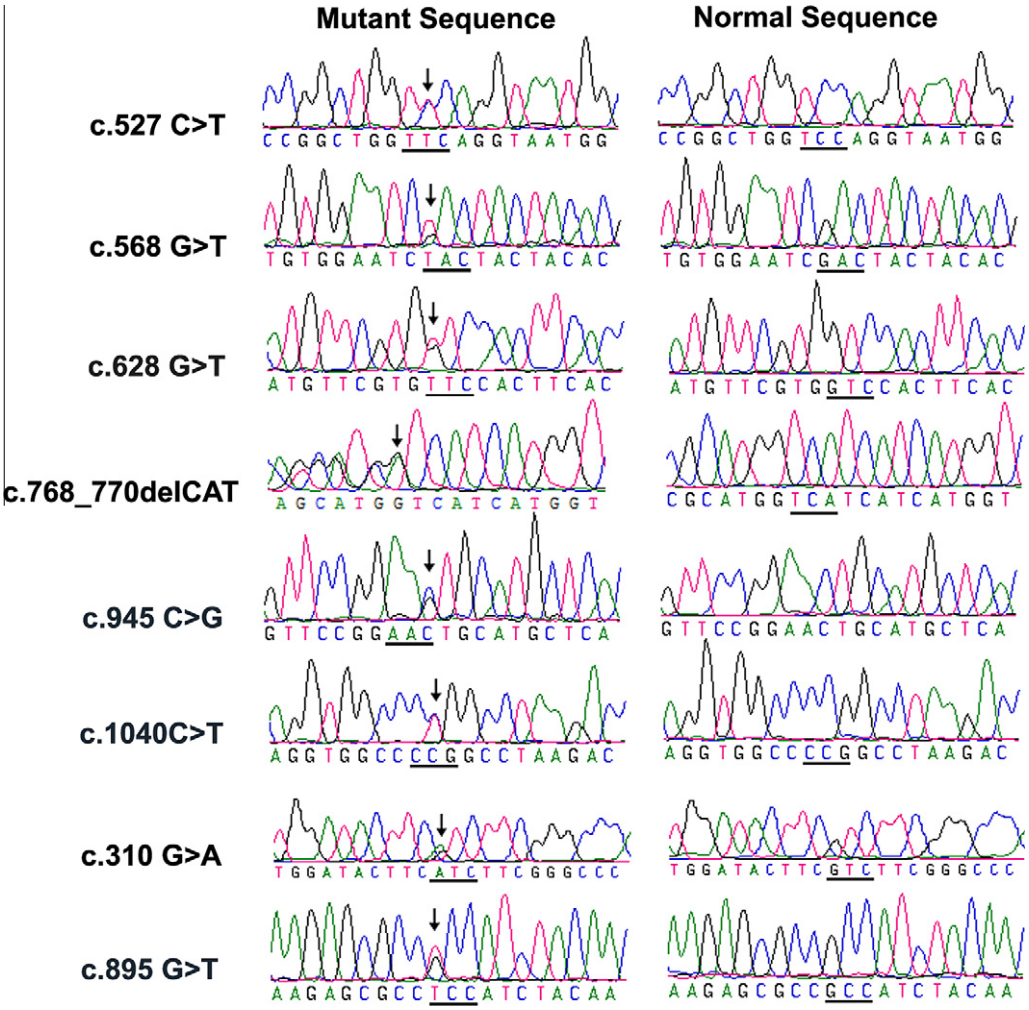

Fig. 1. Sequence chromatography. Eight sequence changes detected in the probands with RP are shown (left column) compared with corresponding normal sequences (right column).

probands but in none of the 384 controls, and the c.895G>T (p.Ala299-Ser) was detected in six of the 248 probands but in only one of the 384 controls ($p = 0.014$) (Table 3).

All 14 probands with heterozygous RHO mutations had clinical symptoms and signs of RP (Table 4). For the six probands with pathogenic mutations, three had adRP and three were singleton cases. For the eight probands with mutations of an uncertain nature, two had arRP and six were singleton cases. For the control individual with the common c.895G>T (p.Ala299Ser) mutation, further ophthalmological examination confirmed that she had completely normal visual function and normal appearing fundus.

4. Discussion

In this study, the entire coding and adjacent intronic sequences of RHO in 248 probands with RP were systemically analyzed by cycle sequencing. Eight heterozygous mutations were detected in

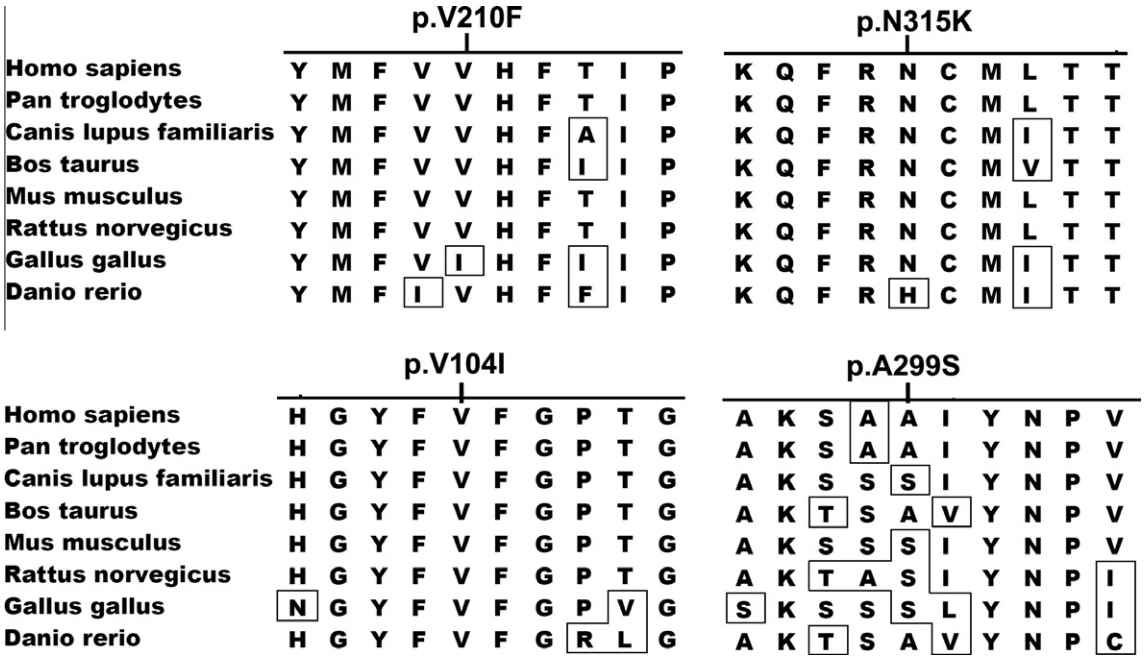

Fig. 2. Protein sequence alignment of eight RHO orthologs. The regions with the novel p.V210F and p.N315K mutations are comparatively conserved, especially in mammals. The region with p.V104I mutation is conserved although this variation is predicted to be benign by PolyPhen-2.

Table 4
Clinical information on individuals with RHO variations.

ID	Variations	Gender	Age (yrs)	Age at onset	Inheritance	First symptom	Visual acuity (right; left)	Fundus change	ERG responses	
									Rod	Cone
	Pathogenic									
Z610180	c.527 C>T	F	40	EC	AD	Poor vision	0.1; 0.06	RP	N/A	N/A
Z610035	c.568 G>T	M	27	NA	Isolated	N/A	N/A	RP	N/A	N/A
Z610132	c.628 G>T	M	5	4	Isolated	Night blindness	0.7; 0.7	RP	Undetectable	Undetectable
Z610113	c.768_770delCAT	F	26	EC	AD	Night blindness	N/A	RP	N/A	N/A
Z610017	c.945C>G	F	28	17	Isolated	Night blindness	0.6; 0.5	RP	N/A	N/A
Z610090	c.1040C>T	M	24	6	AD	Night blindness	1.0; 0.9	RP	Undetectable	Undetectable
	Unknown									
Z610057	c.310 G>A	M	41	38	Isolated	Night blindness	0.4; 0.25	RP	N/A	N/A
Z610187	c.310 G>A	F	5	5	Isolated	Strabismus	0.9; 0.8	RP	Undetectable	Reduced
Z610257	c.895G>T	M	38	25	Isolated	Night blindness	0.7; 0.5	RP	Undetectable	Reduced
Z610082	c.895G>T	F	5	3	Isolated	Poor vision	0.6; 0.6	RP	Undetectable	Reduced
Z610121	c.895G>T	M	36	28	Isolated	Night blindness	0.05; 0.04	RP	N/A	N/A
Z610150	c.895G>T	M	32	22	AR	Reduced vision	0.3; 0.4	RP	N/A	N/A
Z610098	c.895G>T	M	9	2	Isolated	Night blindness	0.2; 0.3	RP[a]	Undetectable	Undetectable
Z610071	c.895G>T	M	10	4	AR	Night blindness	0.5; 0.5	RP	N/A	N/A
NC00296	c.895G>T	F	21	No		No symptom	1.0; 1.5	Normal	Normal	Mildly reduced

EC = early childhood. N/A = not available. LP = light perception.
[a] With RP changes except for pigment deposits.

5.65% (14/248) probands, including 8.11% (3/37) in adRP, 8.00% (2/25) in arRP, and 5.49% (9/164) in isolated RP. These mutations were distributed in every coding exon of RHO. Our study provides a useful clue regarding the actual frequency of RHO mutations in a Chinese population.

Thus far, a number of mutations in RHO have been detected and RHO mutations are a common cause of adRP, accounting for 16.28–28.67% of adRP in Caucasians [7,8,23,24]. However, RHO mutations are much less frequent in Asian patients with RP, accounting for 5.88% of adRP in Japanese populations [25–28], none of 53 adRP

in Indian populations [29], and 4.00% of adRP and 1.98% of all RP in Chinese populations [22,30]. However, it is unknown whether the differences of RHO mutation frequencies are due to ethnic diversity or the methods and strategies used for mutational screening. Nevertheless, the methods used in this study detected more mutations than those used in previous studies, yet, the overall mutation rate of RHO in Chinese patients was significantly lower than reported rates in Caucasian patients. These results provide strong evidence for ethnic variations in the mutation frequency of RHO. This type of ethnic differences in a mutation frequency has been observed with other genetic eye diseases, such as mtDNA mutation in Leber hereditary optic neuropathy [31,32] or CEP290 mutations in Leber congenital amaurosis [33–36], etc.

RHO mutations in singleton cases are rarely mentioned. Recently, Jin et al. analyzed three of the five coding exons of RHO with a denaturing high performance liquid chromatography (dHPLC) based assay and identified five mutations in 3.02% (6/199) patients with simplex or multiplex RP [37]. Gandra also detected one mutation in 48 isolated cases (2.08%) in Indian patients [29]. In this study, RHO mutations were detected in 5.49% (9/164) of isolated RP. Therefore, further analysis of singleton cases in other genes responsible for adRP might enrich our understanding of the mutation spectrum and frequencies of different causative genes for RP. These findings can facilitate the clinical application of mutation-based diagnosis and genetic counseling as well as guide possible interventions such as gene-based therapy.

We do not know whether the c.310G>A (p.Val104Ile) and c.895G>T (p.Ala299Ser) mutations should be considered benign variations or possible disease-causing mutations. Although previous studies have suggested that these two mutations were present in controls and do not cosegregate with RP in family analyses [21,22], they may still play role in retinal degeneration as either a modifier allele or recessive allele because RHO mutations are also responsible for arRP. In addition, digenic mutations in RHO (G174S) and RDS (W316G) have been identified in an isolated Japanese patient with RP [37]. Further analysis of additional patients and other genes may provide additional evidence to clarify the nature of such mutations.

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