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# Genetic markers for retinitis pigmentosa

## 視網膜色素變性的遺傳標誌物

**Objective.** To review recent advances in the molecular genetics of retinitis pigmentosa with emphasis on the development of genetic markers that aids diagnosis and prognosis.

**Data sources and extraction.** Literature search of MEDLINE from 1988 to 2005 using the following key words: 'retinitis pigmentosa', 'rhodopsin', 'RPI', 'RPGR', and 'genetic counseling'. References of two genes—*RHO* and *RPI*—causing retinitis pigmentosa in the Chinese population were reviewed.

**Study selection.** Literature and data related to genetic markers for retinitis pigmentosa.

**Data synthesis.** The genetics of retinitis pigmentosa is complex. It can be sporadic or familial, with heterogeneous transmission modes. Retinitis pigmentosa is associated with nearly 40 chromosomal loci, where 32 candidate genes have been identified. A large number of mutations are known to cause retinitis pigmentosa. But no single mutation alone accounts for more than 10% of unrelated retinitis pigmentosa patients. Genetic tests for retinitis pigmentosa require screening for a consort of mutations in a large number of genes. High throughput screening technology such as denaturing high performance liquid chromatography and automated DNA sequencing should make such tests feasible.

**Conclusions.** Rapid developments in the understanding of the genetics of retinitis pigmentosa have helped to establish genetic tests of clinical value. The complex mode of inheritance nonetheless makes genetic counselling difficult, even in the presence of positive genetic screening results.

### Key words:

Genetic counseling;  
 Genetic heterogeneity;  
 Retinitis pigmentosa

### 關鍵詞：

遺傳諮詢；  
 遺傳多相性；  
 視網膜色素變性

Hong Kong Med J 2005;11:281-8

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**目的：**綜述視網膜色素變性分子遺傳學的最新進展，並着重於對診斷和預測病情發展有助的遺傳標誌物的最新發展動向。

**資料來源與選取：**應用MEDLINE檢索1988至2005年的文獻，以'retinitis pigmentosa'，'rhodopsin'，'RPI'，'RPGR'，和'genetic counseling'為關鍵字，回顧在華裔人口中引致視網膜色素變性的兩個基因：*RHO*和*RPI*的相關文獻。

**研究選擇：**與視網膜色素變性的遺傳標誌物相關的文獻和數據。

**資料綜合：**視網膜色素變性的遺傳學很複雜。該病可以散發，也可以呈家族性聚集，其遺傳方式呈異質性。迄今發現有近40個染色體位點與視網膜色素變性相關，從中已經鑒定出32個候選基因。有大量已知基因突變會導致此病，但是沒有任何一個單獨突變可以解釋超過10%的散發病例。視網膜色素變性的遺傳學檢測須篩選多個基因中的一組突變。高效的篩選技術如變性高效液相色譜法和自動測序法使這種檢測可行。

**結論：**科學家對視網膜色素變性遺傳學的認識已有相當迅速的發展，這些知識有助建立具有臨床價值的遺傳學檢測試驗。儘管如此，即使有呈陽性的遺傳測試結果，此病症複雜的遺傳模式會令遺傳諮詢及預測變得困難。

## Introduction

Retinitis pigmentosa (RP) is a heterogeneous group of inherited progressive retinal diseases. Degeneration of photoreceptor cells leads to the loss of their function and viability.<sup>1,2</sup> Typical fundal changes of the eye include attenuated arterioles, perivascular paravenous and midperipheral bone-spicule pigmentation, and waxy pallor of the optic disc. The bone-spicule pigmentation is due to melanin-containing vesicles in the retinal vascular layer and around the Müller cells.<sup>3</sup> Symptoms usually emerge in adolescence, progressing to legal blindness by middle age and total vision loss in later life. Night blindness is the most common symptom in the early stages, followed by a constricting visual field and, finally, tunnel vision. Myopia is often associated as the disease progresses. Middle-aged patients often have posterior subcapsular cataract and detachment of the vitreous.<sup>2,3</sup> The diagnosis of RP relies on documented progressive loss in photoreceptor function by electroretinography and visual field testing. These techniques are capable of detecting early-stage disease.<sup>1</sup> The amplitudes of the scotopic and photopic b-wave are reduced progressively, averaging 16% to 18.5% of the remaining amplitude per year. There is an implicit time delay between the flash of light and peak of the b-wave. Such clinical features can be variable. The age at onset of symptoms, course of visual impairment, morphological features, and other phenotypic complications can vary greatly, even among members of an affected pedigree. A large proportion of patients will eventually become irreversibly blind. Retinitis pigmentosa affects about 1 in 3500 people worldwide with pan-ethnic occurrence. Asians, including Chinese, show a similar prevalence to Caucasians.<sup>2,3</sup>

Most forms of RP are monogenic with a classical inheritance pattern: 15% to 20% of all cases are autosomal dominant (adRP), 20% to 25% autosomal recessive (arRP), and 10% to 15% X-linked (XLRP). Some families with RP exhibit more complex inheritance patterns: digenic diallelic mode, digenic triallelic mode, and uniparental disomy. In the remaining 40% to 55% of RP, the segregation pattern cannot be established due to an absent family history: such cases are termed sporadic RP.<sup>2,4</sup> The reported frequency of different modes of inheritance shows great variation. A multicentre genetic study in Japan concluded that there may not be significant ethnic differentiation.<sup>5</sup> There are no established data on RP inheritance patterns in the Chinese population, but such data would be of great help in the provision of effective genetic counselling for RP patients.

The most serious form of RP is XLRP.<sup>6</sup> Disease onset is early, progression of visual loss is quick, and blindness often occurs by age 30 to 40 years. The clinical presentation is milder in females than males, probably due to chromosome X inactivation.<sup>2,3</sup> There are also syndromic forms of RP, in which the disease is present as part of a multisystem disorder: Usher's syndrome, Bardet-Biedl syndrome, and Refsum's disease are some examples. Most syndromes demonstrate an autosomal recessive inheritance pattern and various extra-ocular abnormalities such as deafness, polydactyly, obesity, mental retardation, hypogonadism, polyneuritis, and ataxia.<sup>7</sup> This review focuses on non-syndromic forms of RP.

## Prevention and treatment of retinitis pigmentosa

Retinitis pigmentosa can be neither prevented nor effectively treated. Wearing of sunglasses with short-wavelength filters during outdoor activities may reduce discomfort due to glare, but progression of RP is not evidently affected.<sup>8</sup> Vitamin A supplementation has been shown to slightly slow disease progression, as monitored by electroretinography.<sup>9</sup> This benefit can be greatly enhanced by concomitant vitamin E. Contrary to these findings, a study over 4 years revealed no slowing in the rate of decline of disease following a therapeutic dose of docosahexaenoic acid.<sup>10</sup> No clinical improvement in RP has been documented following any form of nutritional supplementation.

Electrical stimulation of the retina by epiretinal implantation of microelectrode arrays may provoke some light perception with no adverse effects in blind patients with RP.<sup>11,12</sup> Such electrical stimulation for phosphenes in the eyes, although small and sporadic, are repeatedly demonstrable in different studies.<sup>12</sup> The ability to see light spots and even identify apparent direction of movement by some blind RP patients with epiretinal implantation of an electrode array device has been reported.<sup>13,14</sup> A similar 6-month study revealed no improvements in visual acuity, visual field, or electroretinography in RP patients treated with retinal electric stimulation.<sup>15</sup> Electrical stimulation of the retina may be a potentially useful treatment approach, but is not appropriate as a retinal prosthesis.<sup>16</sup>

Attention has been focused on appropriate gene therapy for RP following the identification of disease-causing mutations in specific genes associated with RP, principally the rhodopsin (*RHO*) gene.

Some apparent benefit in visual restoration has been obtained through intra-ocular delivery of wild-type *RPE65* as a 'therapeutic gene' to a recessive RP model of dogs with a *RPE65* mutation.<sup>17</sup> In mice defective in the *Prph2*<sup>Rd2/Rd2</sup> gene complex, subretinal injection of a *Prph2* transgene led to generation of outer segment structures and formation of new stacks of discs, and partial electrophysiological correction.<sup>18</sup> Both models utilised recombinant adeno-associated virus as a vector for therapeutic gene delivery. This has become an established gene transfer technique.<sup>19</sup> Although more advances in the gene therapy of RP animal models may eventually lead to trials in human subjects, many technical obstacles remain to be overcome, for example translation inhibition and tissue distribution.<sup>20</sup> Trials of gene therapy for RP in humans may nonetheless take place in this decade.

### Molecular genetics of retinitis pigmentosa

The complexity of RP genetics is reflected by the large number of known or putative RP genes or chromosomal loci. To date, 14 adRP, 16 arRP, and two XLRP genes are known to be associated with RP. Multiple genes have been identified for each mode of segregation (RetNet, <http://www.sph.uth.tmc.edu/RetNet/>). While most known inherited cases of RP are single-gene determined, digenic RP has also been identified to involve mutations in peripherin 2 and Rom 1, encoding their respective membrane proteins.<sup>21,22</sup> Despite variable in gene families, most genes associated with RP encode proteins that are involved in phototransduction, the visual cycle, photoreceptor structure, and photoreceptor cell transcription factors. The functions and the underlying mechanism leading to RP remain unknown for some of these genes (Retina International, <http://www.retina-international.com/>; OMIM, <http://www.ncbi.nlm.nih.gov/OMIM>) [Tables 1-3].<sup>23</sup>

Locus heterogeneity occurs in RP and mutations at many loci can cause the same disease. There is also phenotypic heterogeneity: a single mutation may be associated with substantially different phenotypes within a family or between families, and different mutations in the same gene can cause different phenotypes. Such heterogeneity vividly reflects the unusually complicated pathogenesis. To date, no single gene mutation causes more than 10% of all cases of RP. Mutations of the *RHO* gene and the *RPI* gene occur in approximately 30% of patients with adRP. Linkage studies have suggested that the RP GTPase-regulator (*RPGR*) gene accounts for 70% to 90% of XLRP.<sup>24</sup> The prevalence of disease-causing

mutations in other associated genes is either lower or unknown (Children's Health system and University of Washington, <http://www.genetests.org>) [Tables 1-3].<sup>23</sup> *RHO*, *RPI*, and *RPGR* are the three most prominent RP genes.

#### **RHO (MIM # 180380)**

*RHO*, located on chromosome 3q21-25, is the most common gene implicated in adRP, and accounts for 25% to 30% of all cases in most populations. *RHO* mutations that cause arRP have also been found, despite infrequently, with two cases having been reported.<sup>25,26</sup> More than 100 different missense or nonsense mutations in *RHO* that cause RP have been identified.<sup>27-30</sup> They inevitably lead to the production of aberrant protein variants, with deletion or alterations of only one or a few amino acids. There are also a few truncations. These mutations are scattered in all the three structural domains of rhodopsin: the intradiscal, the transmembrane, and the cytoplasmic domains.

*RHO* P23H was the first gene mutation shown to cause RP. It accounts for 12% of the RP population in the US but a smaller percentage elsewhere.<sup>30-32</sup> All other *RHO* mutations are present in only a small number of patients. It is thus difficult to classify *RHO* mutations relative to clinical data. Unlike wild-type rhodopsin, the expression of P23H resulted in a generalised impairment of the ubiquitin proteasome system, which suggests a mechanism for the degeneration of photoreceptor cells. Disease associated with mutations in this codon results in a relatively mild clinical phenotype of RP and a good prognosis. Interestingly, a survey of affected individuals from 91 European pedigrees did not show the presence of this mutation. P23H-related RP requires phototoxicity and other determinants to be present to have an effect on clinical severity.<sup>33</sup>

Codon 347 at the C-terminus of rhodopsin is another mutational hot spot, with six disease-causing sequence variations (P347T, P347A, P347S, P347Q, P347L, and P347R) identified at this locus. The phenotype of rhodopsin-related RP as a result of mutations involving codon 347 is more severe than that involving codon 23.<sup>30</sup> The C-terminus of the *RHO* gene carries a more-guarded prognosis because the C-terminus of rhodopsin plays a role in cellular transport.

#### **RP1 (MIM # 603937)**

*RP1* gene has been mapped on chromosome 8q11-12 for adRP.<sup>34</sup> Although over 20 polymorphisms in the

**Table 1. Genes causing autosomal dominant retinitis pigmentosa**

Gene	Location	Function	Occurrence
<i>CRX</i>	19q13.32	Photoreceptor cell transcription factor	Rare
<i>FSCN2</i>	17q25	Morphologic structures of photoreceptor cells	Rare
<i>HPRP3</i>	1q21.2	Unknown	Rare
<i>IMPDH1</i>	7q32.1	Regulate the cell growth	3-5%
<i>NRL</i>	14q11.2	Photoreceptor cell transcription factor	Rare
<i>PDC</i>	1q25-32.1	Visual transduction cascade	Unknown
<i>PRPF8</i>	17p13.3	Unknown	Unknown
<i>PRPF31</i>	19q13.42	Pre-mRNA slicing	15-20%
<i>RDS</i>	6p21.2	Photoreceptor structure	5-10%
<i>RHO</i>	3q22.1	Visual transduction cascade	25-30%
<i>ROM1</i>	11q12.3	Photoreceptor structure	Rare
<i>RP1</i>	8q12.1	Transcription factor	5-10%
<i>RP9</i>	7p14.3	Unknown	Unknown
<i>RP17</i>	17q22	Pre-mRNA slicing	Unknown

**Table 2. Genes causing autosomal recessive retinitis pigmentosa**

Gene	Location	Function	Occurrence
<i>ABCA4</i>	1p22.1	Catabolic function in the retina	Rare
<i>CNGA1</i>	4p12	Visual transduction cascade	Rare
<i>CNGB1</i>	16q13	Visual transduction cascade	Unknown
<i>CRB1</i>	1q31.3	Transcription factor	Rare
<i>LRAT</i>	4q32.1	Retinoid metabolism	Unknown
<i>MERTK</i>	2q13	Disc shedding	Rare
<i>NR2E3</i>	15q23	Ligand-dependant transcription factor	Rare
<i>PDC</i>	1q25-32.1	Visual transduction cascade	Unknown
<i>PDE6A</i>	5q33.1	Visual transduction cascade	3-4%
<i>PDE6B</i>	4p16.3	Visual transduction cascade	3-4%
<i>RGR</i>	10q23.1	Retinoid metabolism	Unknown
<i>RHO</i>	3q22.1	Visual transduction cascade	Rare
<i>RLBP1</i>	15q26.1	Retinoid metabolism	Unknown
<i>RPE65</i>	1q31.2	Retinoid metabolism	2%
<i>SAG</i>	2q37.1	Visual transduction cascade	Rare
<i>TULP1</i>	6p21.31	Photoreceptor cell transcription factor	Rare
<i>USH2A</i>	1q41	Retinal development	4-5%
<i>RP22</i>	16p12.1p12.1	Not cloned	Rare
<i>RP25</i>	6cen-q15	Not cloned	Rare
<i>CERKL</i>	2q31-q33	Ceramide metabolism	Rare
<i>RP28</i>	2p16-p11	Not cloned	Rare
<i>RP29</i>	4q32-q34	Not cloned	Rare

**Table 3. Genes causing X-linked retinitis pigmentosa**

Gene	Location	Function	Occurrence
<i>RP2</i>	Xp11.23	Protein folding	8%
<i>RPGR</i>	Xp11.4	Protein transport	70%
<i>RP6</i>	Xp21.3-21.2	Not cloned	Unknown
<i>RP23</i>	Xp22	Not cloned	Unknown
<i>RP24</i>	Xq26-27	Not cloned	Unknown

*RP1* sequence may be related to RP, seven definite *RP1* disease-causing mutations have been identified: R677X, Q679X, G723X, 2332delG, 2336-2337delCT, 2433del5bp, and 2435del4bp. All are contained within a 442-nucleotide region in the first third of the coding region.<sup>34-39</sup> The *RP1* protein may be able to tolerate

considerable sequence variation. Photoreceptor degeneration results only in truncation of the *RP1* protein. Approximately 7% of all cases of RP are estimated to be due to *RP1* mutations. Two mutations, R677X and Q679X, account for almost 60% of all *RP1* mutations that cause RP.

The nonsense mutation, R677X, is a common mutation in adRP. In the US, it causes RP in approximately 3% of adRP patients. R677X is a cytosine-to-thymine transition at a hypermutable CpG dinucleotide. In the human genome, 60% to 90% of CpG dinucleotides are methylated. The propensity of transformation of 5-methylcytosine into thymine through spontaneous deamination accounts directly

for the quick mutation rate or higher mutability than usual. Such a mutational mechanism likely accounts for the high recurrence of the R677X. In a large adRP pedigree, R677X was identified in all affected members.<sup>36</sup> The mutation was predicted to lead to rapid degradation of the mRNA or to the synthesis of a truncated protein lacking approximately 70% of its original length. Another two nonsense mutations, Q679X and G723X, and four deletion mutations, 2332delG, 2336-2337delCT, 2433del5bp, and 2435del4bp, also cause frameshifts and introduce premature termination codons. All these mutations result in the formation of a severely truncated protein approximately one third the size of the wild type. Although these seven mutations each result in a shortened *RPI* polypeptide with similar size, the phenotype of the affected individuals, such as the age of development of symptoms and disease progress, varies greatly. Environmental factors or modifying gene effects may modulate the contribution of *RPI* mutations to phenotypic manifestations.

#### **RPGR (MIM #312610)**

The *RPGR* gene was cloned on chromosome Xp21.1 in 1996. Since then, 77 mutations of the gene scattering in exons 1-14 and ORF15 have been described.<sup>40-42</sup> A normal *RPGR* transcript is necessary for normal retinal function in humans. Most mutations can be predicted to cause a premature termination of translation. It is noted that most *RPGR* missense mutations occur in exons 1-10, which encode a polypeptide domain highly homologous to chromosome condensation 1 (RCC1). A mutation hot spot has been found in exon ORF15. In a British study, 81% (38 of 47) individual XLRP patients harboured *RPGR* mutations in exon ORF15. Investigation of phenotype-genotype correlation is difficult because most *RPGR* mutations are unique to single families. When compared with patients with sporadic RP or carrying mutations in other RP genes, RP patients with *RPGR* mutations have smaller visual fields and more severely reduced full-field electroretinography amplitudes.<sup>41-43</sup>

#### ***RHO*, *RPI*, and *RPGR* mutations in the Chinese population**

We studied *RHO* and *RPI* gene mutations in the local population in order to identify common mutations in Chinese patients with RP and to determine whether these mutations could be used to aid pre-symptomatic diagnosis and prognosis.<sup>32</sup> Individual patients of any pattern of inheritance with a typical history and clinical features of RP were recruited. A complete

ophthalmoscopic examination, including fundus examination, was performed. Family history and clinical features were documented. Family members with and without RP were invited to participate in the study. Control subjects were all unrelated, aged above 60 years, with no systemic disease or family history of RP. A full ophthalmoscopic examination was likewise performed to exclude subjects with any eye disease, except mild senile cataracts that occur in almost all people over the age of 60 years.

The entire coding region and exon splice sites of *RHO* and *RPI* in 173 RP patients and 190 controls were examined for sequence changes using polymerase chain reaction and direct DNA sequencing. A subset of these study subjects has been previously reported.<sup>32,44</sup> In *RHO*, one nonsense mutation, 5211delC, and one missense mutation, P347L, were identified: they accounted for 1% (2/173) RP patients. Each sequence alteration was found in one RP patient. 5211delC may destroy the C-terminal localisation signal and lead to mis-sorting of the rhodopsin polypeptide, as the negatively charged final 22 amino acids containing six phosphorylation sites are replaced by a 32 amino acid positively charged nonsense sequence with only two phosphorylatable residues. In *RPI*, one subject with a mutation, R677X, was identified, giving a mutation frequency of 0.6% in the Chinese population, lower than the 2% frequency reported in the US. One control subject heterozygous for a *RPI* truncation mutation at codon 1933, R1933X, was identified. This suggests that a normal level of the C-terminal 224 amino acid of *RPI* is not essential for normal eye function. Meanwhile, a 1-bp deletion at codon 1053 has been proved to cause RP.<sup>45</sup> The polypeptide, or part of it, between the amino acids at 1053 and 1933, is therefore essential for normal photoreceptor function. Two missense changes were also found: D984G and R872H. Like R1933X, both are so far known to exist only in the Chinese population. R872H might confer a protective effect against RP because it is more frequent in the controls than in RP patients ( $P < 0.05$ ). Overall, the frequencies of *RHO* and *RPI* mutations among RP patients in the Chinese population are less than those reported in other populations.

Mutations of the *RPGR* gene in Chinese RP patients have been studied by other research groups.<sup>43,46</sup> Two novel truncations, E332X (G1053T) in exon 9 and 1536delC in exon 12, were each found in one Chinese family. Both mutations co-segregated with RP in respective families and caused severe retinal complications and visual impairment. E332X and more than 29 mutations clustered in the highly

conserved RCC-1-like domain (RLD) in the N-terminal half of the RPGR protein, suggesting this domain to be of functional importance.<sup>43</sup> Another truncation that also caused severe RP and was present only in the Chinese population was a 28bp deletion in exon 7.<sup>46</sup>

### Genetic markers for retinitis pigmentosa

Genetic testing for RP remains controversial. Determination of the exact inheritance trait is difficult and diagnosis can be equivocal. Genetic testing of blood relatives of RP patients may nonetheless identify mutation carriers before they become symptomatic. The large number of RP genes, each accounting for a certain small proportion of RP patients, places a heavy burden on laboratories when screening for the underlying RP mutation. Some mutations occur more commonly in certain populations, such as *RHO* P23H, *RHO* P347L, and *RPI* R677X in Caucasians. They warrant screening in patients with dominant RP, although their occurrence in Chinese is lower than Caucasians.<sup>27-29,34,37,44</sup> In the case of *RPGR*, it is technically feasible to screen for mutations in possible and probable X-linked families, isolated affected males, and potential XLRP-carrier females. Exon 1-14 and *OFR15* are hot spots for mutation screening.<sup>24,41,43</sup>

No single mutation, on its own, accounts for more than 10% of unrelated RP patients. In addition to the mutations mentioned above, genetic tests for RP require screening for a set of mutations in a number of genes. The availability of high throughput screening technology such as denaturing high performance liquid chromatography and direct DNA sequencing makes genetic tests feasible.<sup>47</sup> Improvement in manufacturing processes and new high-power computation programs have been applied to capillary electrophoresis systems for high throughput detection of SNPs or mutations in gene sequences.<sup>48,49</sup> Advanced but simplified microarray systems are also available for rapid testing of a large number of specimens.<sup>50,51</sup> In routine clinical laboratories, basic facilities and equipment can be enhanced for high-throughput procedures, such as conformation sensitive gel electrophoresis, denaturing high performance liquid chromatography, and direct sequencing.<sup>47,52,53</sup> Priority will be given to screening for some particular gene mutations if the mode of inheritance is known. In Hong Kong, a genetic testing service is available for diagnosis of RP involving the *RHO* and *RPI* genes. Nonetheless these two genes together account for less than 5% of all RP cases in the local Chinese population.<sup>23,54</sup>

Retinitis pigmentosa caused by gene mutations may

be frequent in certain isolated or consanguineous populations, although the prevalence and presentation of RP show no ethnic specificity. In our studies, the prevalence and pattern of *RHO* and *RPI* mutations in the Chinese population differ to those in Caucasians. Mutations in other RP genes that may be more often attributed to affected Chinese or unidentified RP loci still exist. Before genetic screening for RP can be established for a specific population, relevant genetic epidemiological data for that population must be available. This should include the disease prevalence, mutation patterns, and frequencies in the disease-associated genes, and patterns of inheritance. The carrier frequency of each RP gene should be known before estimates of risk occurrence can be made.<sup>54</sup> The predictive value of specific tests should be established and internal and external quality assurance programmes made available.

### Genetic counselling

Once a patient's RP phenotype is identified, risks to family members can be established based on the mode of inheritance and availability of molecular genetic testing. In an adRP family, the risk to siblings depends on the genetic status of the proband's parents. If one of the proband's parents has a mutant allele, then the risk to the siblings of inheriting the mutant allele is 50%. Individuals with adRP have a 50% chance of transmitting the mutant allele to each child. In arRP families, siblings have a 25% chance of being affected, a 50% chance of being unaffected, and a 25% chance of being a carrier. Once an at-risk sibling is confirmed unaffected, the chance of his/her being a carrier increases to 66.7%. All offspring of the proband are obligate carriers. In an X-linked recessive RP family, several possibilities regarding the mother's carrier status need to be considered if the pedigree has an affected isolated male. The risk to siblings also depends on the genetic status of the proband's mother. All daughters of the affected male are carriers, but no son is affected. For an X-linked dominant RP family, the risk to the siblings of a proband depends on the genetic status of the parents. Affected males will transmit the mutation to all female children but not male. Affected females will have a 50% chance of transmitting the mutation to their own children (sons who inherit the mutation will be affected; daughters will have a range of possible phenotypic expression).

Clinical severity and disease phenotype often differ among individuals with the same mutation regardless of mode of inheritance; thus, age of onset and/or disease progression cannot be predicted. In

patients with a clinical diagnosis of sporadic RP, prediction of inheritability is difficult even with a positive result from gene testing. Alternatively, sporadic RP patients can be referred for genetic counselling for arRP or XLRP: most will have arRP or XLRP. Genetic counsellors should always be cautious of the complex and heterogeneous inheritance patterns of RP, which can be sporadic, classical Mendelian, non-Mendelian, and unconventional. Genetic counselling of patients, mutation carriers, and their family members based on genetic test results remains difficult.

Genetic counselling depends on an accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing. It is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders that helps them make informed medical and personal decisions. Once the pathogenesis of RP is understood, and preventive measures and treatment are available, genetic tests that help in early and pre-symptomatic diagnosis will be immensely useful for genetic counselling.

## Acknowledgement

This paper was supported in part by a direct grant 2040993, Medical Panel of the Chinese University of Hong Kong.

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