• Review Article •

Genetic, environmental and other risk factors for progression of retinitis pigmentosa

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Abstract

● Retinitis pigmentosa (RP) is a commonly inherited disease of the retina, which is characterized by progressive loss of visual function due to specific genetic mutations. There are many risk factors that may have effect on the progression of RP, such as inheritance patterns, genotype, gender, age, smoking, physical activity, and other demographic and environmental factors. Baseline visual field conditions, changes of ellipsoid zone, photoreceptor layer thickness, and choroidal structure are reported to be the phenotype risk factors for RP progression. Moreover, aqueous flare and high-sensitivity C-reactive protein are probable inflammation biomarkers for assessing the progression of RP. Increased oxidative stress is considered to be one of the potential factors for the existence of RP. The risk factors can be combined to form a corresponding prediction model to predict disease progression. This review is to summarize the current literature that studies the genetic, environmental, phenotypic, demographic, inflammatory and other risk factors of RP progression and discuss the most reliable risk factors that could provide predictive models.

● **KEYWORDS:** retinitis pigmentosa; risk factor; progression; genetics; phenotype; inflammation; prediction

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INTRODUCTION

Retinitis pigmentosa (RP) [Online Mendelian Inheritance in Man (OMIM) ID 268000] is a group of inherited retinal degeneration diseases resulting from progressive loss of rod photoreceptor cells, followed by cone photoreceptor cells[1]. Individuals with RP often endure impaired night vision and progressive vision loss. Finally, complete blindness may occur when the visual field defect involves the macular area[2]. The global prevalence of RP is 1/4000[3]. Patients with RP can be divided into autosomal dominant (AD), autosomal recessive (AR) and X-linked inheritance based on their family history, as well as a large majority without family history of disease appear to be isolate cases. In addition, progression of RP can vary among different types. Also, studies have identified several genetic, environmental, phenotypic, demographic, inflammatory and other risk factors for a different RP progression. The potential benefit of discovering these risk factors is the ability to predict disease progression of RP, which can provide new ideas for the efficacy and safety evaluation of new therapies. Nowadays, diagnostic technology is developing rapidly, genetic and molecular diagnostic technologies is advanced. And new risk factors for disease progression are gradually being discovered, but there is still no comprehensive prediction model for progression of RP. Our aim is to summarize the current literature that studies the genetic, environmental, phenotypic, demographic, inflammatory and other risk factors of RP progression in the review. Moreover, we discuss the most reliable risk factors that could provide predictive models.

Definition of Progression in Retinitis Pigmentosa As RP is a slow, progressive disease, it is hard to make an accurate definition for its progression. In earlier studies, visual acuity, electroretinography (ERG), and the visual field (VF) test have been commonly used to monitor RP progression. However, there are limitation with these examinations as evaluation indicators. For example, many patients with RP still remain quite satisfactory central corrected vision in the late period of the disease. On the contrary, evaluation by ERG generally diminishes years before subjective symptoms begin. And for VF test, considerable fluctuations will have impact on the results due to its subjectivity. Therefore, in recent years, more and more researches focus on objective measurements to evaluate the severity of RP. Spectral-domain optical coherence tomography (OCT) is widely used to detect retinal structure in lots of diseases. Previous OCT studies in RP have showed that the structural changes correlated well with retinal function,

measurements of ellipsoid zone (EZ) width and EZ area can serve as metrics of disease severity and progression[4-5]. Retinal layer thickness measured by OCT has also been reported to coincide with the functional evaluations[6-7].

Fundus autofluorescence (FAF) imaging is another objective measurement to observe retina changes at the level of the retinal pigment epithelium (RPE)/photoreceptor complex. It is now an useful tool for evaluating various retinal disorders[8-9]. High autofluorescence (AF) signal intensity indicates the excessive accumulation of lipofuscin or other fluorophores, and low AF signal intensity indicates the loss or atrophy of RPE[10]. Some researchers think AF ring is a transition between abnormal and normal retinal area, with function being relatively normal in side of the ring, reduced within the ring and absent outside the ring[11]. In many RP patients, AF ring presents at the parafoveal area[12]. Previous studies report that the amplitudes of pattern ERG was significantly correlated with the size of the AF ring, and wide-field AF imaging could reflect the presenting scotoma and remaining VF in RP patients[13-14]. A recent study has developed a novel method to objectively evaluate the AF ring through binarization processing, and the authors thought the quantitative analysis of the AF ring could serve as a monitoring tool for RP progression[15].

Although there are more and more new methods to detect RP progression, the most sensitive method has not been established. A good monitor should have high sensitivity that enables to detect minor change easily and reproducibly.

Genetic Risk Factors

Inheritance patterns Whether inheritance patterns have impact on the progression of RP is not determined, however, more and more evidence shows that inheritance pattern is an important risk factor. Patients with RP can be genetically typed by family history into different inheritance patterns, such as AD-RP, AR-RP, and X-chromosome linked forms, as well as a large group of patients appear to be isolate cases. Xu *et al*[16] summarized during a follow-up period of up to 29y (average 12y) and found that there was no statistically significant difference in the annual VF loss rate between different genetic patterns. The annual incidence of AR inheritance is estimated to be 10.3%, X-linked inheritance is 7.2%, and AD inheritance is 2.7%. Even so, it can be seen from the results that AR-RP has tendency to lose VF more quickly than the other two genetic subtypes. The previous study by Sandberg *et al*[17] also testifies to this trend. It is estimated that the annual decrease in the rate of AR-RP due to the usherin (*USH2A*) gene is 7.0%, X-link RP due to the mutations of the RP GTPase regulator (*RPGR*) gene is the 4.7%[18], and AD-RP with rhodopsin (*RHO*) mutations is 2.6%[19]. However, Sayo *et al*[20] cannot confirm that different genetic patterns have different rates of progression in RP because of the relatively small sample size, or maybe the short-term follow-up.

Even if the causative gene is the same, the progression will be different due to different inheritance types. A multi-center cohort study[21] in Japan reported that the phenotypes of RP1 gene-associated retinal dystrophies varied with different inheritance patterns. RP1 gene has been associated with both AD-RP and AR-RP[22]. The age at onset and clinical course of visual acuity in the two phenotypes were significantly different, the age at onset was earlier in patients with AR-RP, also visual acuity started to worsen around their 20s and reached severe visual dysfunction by their 40s instead of good visual acuity preserved in patients with AD-RP until their 50-60s. The same result applies to VF, multimodal retinal imaging, and ERG findings.

Genotype Many studies have shown that genotype plays an important role in RP progression. Up to now, ninety-three genes and loci (https://sph.uth.edu/retnet/, last updated September 29, 2021) have been identified to be associated with RP, mostly related with phototransduction cascade, visual cycle and photoreceptor structure.

Phototransduction is a biochemical process in photoreceptor neurons that converts absorption of light into electrical activity. It has been found that several gene families participate in the biochemical pathway, such as rhodopsin, transducin, and cyclic nucleotide gated ion channels. Photoreceptor viability is very sensitive to disturbation in phototransduction. Mutations in genes that encode phototransduction proteins can cause photoreceptors to degenerate, affecting the phototransduction cascade, and eventually leading to the progressive death of photoreceptors. Animal experiments verified that the RP phenotype caused by the phosphodiesterase 6B (*PED6B*) gene mutation appeared segregated in different sexes. Female mice progressed faster than the male, and pointed out that female is potential risk factor in RP of *PED6B* gene mutation[23]. This result needs to be confirmed in future clinical studies. *RHO* mutations account for 30%-40% of AD-RP, affecting the amino acidic sequence of the rod-specific protein rhodopsin. Severity and rate of progression are associated with specific *RHO* mutations. For example, the argine to lysine change at codon 135 (Arg-135-Lys, or R135L) and the arginine to tryptophan change at codon 135 (Arg-135-Trp, or R135W) mutations (cytoplasmic end of the third rhodopsin transmembrane helix) result in diffuse, severe disease. And, R135W causes more severe and more rapidly progressive RP than R135L. The proline to alanine change at codon 180 (Pro-180-Ala, or P180A) and the glycine to arginine change at codon 188 (Gly-188-Arg, or G188R) mutations present a mild phenotype with regional variability and diffuse disease of moderate severity[24]. Fascin actin-bundling protein 2 (*FSCN2*) gene encodes the

initiation protein for the formation of retinal outer segment. peripherin 2 (*PRPH2*) and cadherin related family member 1 (*CDHR1*) work together to play a signal transduction role during the formation of outer segments and stabilize its morphology[22]. There are other genes such as retinal outer segment membrane protein 1 (*ROM1*) and prominin 1 (*PROM1*) that participate in this complex process. Changes in the number and type of mutations of any gene will cause variations in the phenotype of RP and affect its pathological process. Studies have reviewed that the more significant the changes in the protein level encoded by the *PRPH2* and *ROM1* gene, the earlier the onset of the disease and the more severe the pathological changes[25].

Visual cycle is a complex process that requires the participation of proteins encoded by a variety of genes, such as retinoid isomerohydrolase rpe65 (*RPE65*), atp binding cassette subfamily A member 4 (*ABCA4*), retinol dehydrogenase 12 (*RDH12*) and retinol binding protein 3 (*RBP3*). Case reports showed that, the progress of RP mediated by *RPE65* gene mutation was slower within two years compared with other mutation evaluated by FAF and the width of EZ[26]. However, large sample studies need to confirm this trend subsequently.

USH2A is a common causal gene of RP, coding for the transmembrane protein Usherin which is expressed in the cilia region in the photoreceptor cells. *USH2A* plays important roles in the development and homeostasis of the retina and inner ear. RP patients with *USH2A* gene mutations were divided into two groups: syndromic and non-syndromic. Comparing their average age of onset, it was found that the onset of non-syndromic type was significantly later, and the difference between the two was close to 10y[27-28]. Not only that, the rate of vision loss and change of mean defect (MD) value of non-syndromic type were also slower, and the degree of VF damage was relatively low.

Gene variants Diagnosis of the molecular genetics of RP should be accompanied by analysis of number of variants. There are many genes related to RP, even if the disease-causing genes are the same, the mode of disease progression and rate of deterioration may be different. It is because many genes have different variants, which will lead to different pathogenic phenotypes. For example, Jespersgaard *et al*[29] found that clinical examinations of 56 RP patients caused by *MER* proto-oncogene, tyrosine kinase (*MERTK*) gene mutations showed severe phenotypes, however, the remaining phenotypes were milder, which may be due to the different number of variants in different patients. We can search hundreds of genes related to human RP in the Disgenet database (https://www.disgenet.org/search) alone, which integrates disease-related genes based on literature and multiple databases mining, and each gene has many variants, so there will be more variants affecting RP. We show the top 25 genes according to gene-disease association scores and their single nucleotide polymorphisms (SNPs) in Table 1.

Phenotypic Risk Factors

Baseline mean defect If the baseline level of the visual field is different, the disease progresses at different speeds. It can be understood that different disease stages will have different disease progression rates. In order to determine whether baseline MD would affect the deterioration rate of macular sensitivity, Sayo *et al*[20] divided RP patients into two groups with initial MD ≥-17.9 dB and <-17.9 dB for the study, namely the less advanced group and the advanced group. The results showed the former progression (-0.01 dB/y) is much significantly slower than the latter (-0.67 dB/y). Since the central field of vision is still preserved in the late stage, this result is considered reasonable.

Ellipsoid zone The progression rate of RP is slowing down when the progression of disease involves the fovea. With the advanced development of multimodal imaging, clinicians may have access to following the microstructural changes in RP patients, and the changes can be seen in a shorter time[30-31]. OCT images in which the width of the ellipsoid zone line can monitor progression over time. Furthermore, the wider the EZ width, the faster the disease progresses. Sujirakul *et al*[30] observed that patients with narrower EZ (<3000 μm) had a significantly lower average structural progression rate compared to wider EZ (>3000 μm). Another study[32] concluded that the longer the third high-reflectance band in OCT, the better the vision for patients with the same thickness of retina. It is the same band named as the “the second band” *via* SD-OCT determination, which is now termed ellipsoid zone[33]. A systematic review showed that the width of EZ was the most reliable and sensitive biomarker for detecting disease progression with outstanding reproducibility and visual function correlation[34].

Photoreceptor layer thickness The main pathological feature of RP is changes in photoreceptor and retinal pigment epithelium complex, structural changes will affect the corresponding functions, which refers to the visual function here. Still, the focus of many studies is to clarify the correlation between visual function and structure in RP. Sandberg *et al*[32] concluded that visual acuity of patients with RP who had a thinner central retina (indicating photoreceptor layer) tended to be poorer. Nguyen *et al*[35] also confirmed through long-term follow-up that the thickness of the photoreceptor and retinal pigment epithelial in the macula region was significantly related to best-corrected visual acuity (BCVA), even was a potential effective outcome to replace BCVA in the future. According to the research of Rangaswamy *et al*[7], a simple linear model can reasonably describe the relationship between

Table 1 Twenty-five genes closely related to human RP

Gene	UniProt ID	Gene full name	Gene-disease association score	Numbers of SNPs	First time reported	Last time reported
C8orf37	Q96NL8	Chromosome 8 open reading frame 37	0.95	2	2012	2016
PDE6A	P16499	Phosphodiesterase 6A	0.9	19	1995	2019
PDE6B	P35913	Phosphodiesterase 6B	0.9	8	1992	2019
RPGR	Q92834	Retinitis pigmentosa GTPase regulator	0.8	23	1995	2019
RPE65	Q16518	Retinoid isomerohydrolase rpe65	0.8	5	1998	2019
CRX	O43186	Cone-rod homeobox	0.8	5	1997	2018
PDE6G	P18545	Phosphodiesterase 6G	0.72	0	1997	2010
LRAT	O95237	Lecithin retinol acyltransferase	0.71	1	2007	2018
RHO	P08100	Rhodopsin	0.7	38	1978	2020
CRB1	P82279	Crumbs cell polarity complex component 1	0.7	54	1999	2019
USH2A	O75445	Usherin	0.7	49	1998	2019
IMPDH1	P20839	Inosine monophosphate dehydrogenase 1	0.7	23	2002	2020
MERTK	Q12866	Mer proto-oncogene, tyrosine kinase	0.7	14	2000	2019
EYS	Q5T1H1	Eyes shut homolog	0.7	5	2005	2019
ABCA4	P78363	Atp binding cassette subfamily a member 4	0.7	3	1998	2019
ROM1	Q03395	Retinal outer segment membrane protein 1	0.7	2	1992	2017
GUCY2D	Q02846	Guanylate cyclase 2D, retinal	0.68	15	2005	2016
CNGB1	Q14028	Cyclic nucleotide gated channel subunit beta 1	0.68	6	2001	2019
RPGRIP1	Q96KN7	Rpgr interacting protein 1	0.68	1	2004	2017
NRL	P54845	Neural retina leucine zipper	0.67	1	1999	2017
RDH12	Q96NR8	Retinol dehydrogenase 12	0.66	7	2007	2019
RBP3	P10745	Retinol binding protein 3	0.66	8	1990	2015
CLRN1	P58418	Clarin 1	0.66	2	2002	2019
SPATA7	Q9P0W8	Spermatogenesis associated 7	0.65	1	2009	2018
SAG	P10523	S-antigen visual arrestin	0.65	1	1985	2018

the product of the thickness of the outer segment (OS) and the outer nuclear layer (ONL) and the thickness of the OS versus the visual field loss. That is to say, the number of photoreceptors decreases as the sensitivity of the local retina decreases, and a linear model can be used to simulate the downward trend.

Choroidal structures Structural changes in the choroid will affect the progression of RP. According to the reports, compared to the control group, the choroidal blood flow in RP patients decreased by 26%[36], as same results as the study of choroidal capillaries density[37]. Preliminary studies in animal models of RP had shown that loss of choroidal capillaries did exist, and decreased blood circulation in the foveal choroid caused death of cone cells[38-39]. The choroidal changes that occur in RP are confirmed by the above clinical and animal experiments. In addition, the relationship between disease progression and structural changes has also been studied by Egawa *et al*[40]. They took the choroidal area under the fovea as the observation target and set an observation range of 1500 μm. Finally, they found that the choroidal structure in RP was significantly related to the BCVA, MD, mean sensitivity (MS), EZ width, and central foveal thickness (CFT)[40]. While, another study suggested that the reduction of choroidal blood flow, rather than the change of its structure, is closely related to the structural changes and functional decline of the RP macular region[41].

Demographic and Environmental Risk Factors

Age There are various opinions on the relationship between age and RP progression. Some studies believe that it is influential, while the other does not draw relevant conclusions. Studies[30,42] show no difference in the effects of different ages on the rate of disease progression, and this result may be caused by selection bias. For example, children who are seriously ill are easily diagnosed, while children who are mildly ill are difficult to detect or invisible. As we know, a minority of studies addressed the effect of age on RP. Current studies have found that the age of onset of RP varies, and Wert *et al*[43] reported that the age of onset of autosomal dominant RP can even be as late as 50 years old. But generally speaking, the earlier the manifestations of RP appear, the faster the disease progresses[22]. Therefore, discussing the relationship between age and RP progress is currently challenging.

Gender The same as the result of age, from the great majority of reports, the average MD decreasing rate which indicates progression of RP is not related to gender. Among individuals who are legal blindness which heralds the advanced stage of the disease, the impact of gender on disease progression was statistically significant. Compared with women, the risk ratio for men is 3.03[16]. However, the study failed to reach the same conclusion in the early stage. Such an interesting finding may indicate that male patients in the advanced stages of the disease lose their visual field more quickly. Other studies[20,42] did

not reach the conclusion of this difference, possibly because patients were not divided into less advanced or advanced group. Therefore, this difference has not been captured.

Smoking As we all know, smoking as the most common and important environmental factor always affects human health. It is not only a risk factor for many systemic diseases, but also an inducing factor for many eye conditions[44]. Therefore, smoking may also affect the progression of RP. The way to induce those disease may be through exacerbating oxidative stress. Campochiaro and Mir[45] reviewed the mechanism of cone cell death and proved that it was related to oxidative stress. Thus, Oishi *et al*[46] hypothesized that smoking might also affect the disease progression of RP, especially when it involves the cone-rich macular area. Finally, they discovered that smoking was an independent related factor of poor visual acuity, and might affect the course of RP, causing it to develop more rapidly in a worse direction.

Diet Dietary intake of nutritional supplements may delay the onset of RP. According to observations in many clinical studies, nutritional supplements or indications for patients with retinal dystrophy are usually effective in preventing the progression of RP. Berson *et al*[47] confirmed that supplementation of mixed formulas of nutritional supplements such as vitamin A in the first two years had been shown to slow down the process of RP. Sofi *et al*[48] assessed the dietary status of 56 RP patients for the first time, and found those with high vitamin A intake had a higher onset age compared to individuals who reported low intake. Indeed, since proper handling of vitamin A during phototransduction and visual cycle may be disrupted by genetic abnormalities in a large group of patients with RP, as far as the progression of RP is concerned, the intake of nutrients in the diet will also significantly affect it. Possibly, the dietary pattern of these patients represented a therapeutic approach for the disease presently until further researches clarified a reasonable dietary intake. Although, a study[49] systematically reviewed four randomized controlled trials and proved that dietary supplements, such as vitamin A or docosahexaenoic acid (DHA), could not prevent progression of vision loss. And, it must be noted that improper use of dietary supplements may cause adversary effect. For example, male smokers receiving β-carotene supplements had significantly increased risk of lung cancer. Prostate cancer incidence and mortality were increased in male alcohol users consuming the supplement[50].

Physical activity The effect of physical activity on the progression of RP has not been studied in depth. But it is well known that exercise has a positive effect on both physical and mental health. Previous studies have also suggested exercise is beneficial for prevalent eye diseases such as age-related macular degeneration (AMD)[51] and cataract[52]. Because exercise suggested a neuroprotective effect by proving that it was conducive to the enhancement of memory and promoted the regeneration of hippocampal nerves[53]. Some scientists hypothesized that it had a protective effect on the photoreceptor cells of RP, and finally verified that this was indeed the case based on mouse models[54]. On the clinical side, scientists reported that RP patients are less physically active than normal population, but the relationship between the amount of exercise and the progression of the disease is not clearly indicated[55]. Later, Levinson *et al*[56] used NEI-Visual Function Questionaire-25 as an evaluation method to measure visual function scores, the results showed that people with more physical activity tended to self-report higher visual function scores. However, these studies are still confined to retrospective and other shortcomings.

Inflammatory Factors Inflammation is a response of the immune system in response to harmful stimulus caused by a variety of factors, primarily pathogens, cell damage, and toxic metabolites. Excessive activation of inflammatory cells can produce many inflammatory cytokines or chemokines which can exert cytotoxicity and exacerbate a variety of eye diseases, also lead to the development or progression of RP. Studies have been confirmed that elevated inflammatory cytokines or chemokines in RP are associated with disease progression and with innate and acquired immunity[57]. However, which factor is the most specific mechanism leading to the pathogenesis or progression of RP remains to be further studied.

Intraocular inflammation Inflammation in the eye may be a factor in the rapid progress of RP, and the absence of inflammatory product aqueous flares may keep the vision and VF of RP patients at a relatively stable level in short term. Numerous researches have shown that pathological changes in RP can be placed in relation to chronic intraocular inflammation. It was found that inflammatory cells and pro-inflammatory cytokines significantly increased in vitreous of RP patients, which supported this view[58]. Murakami *et al* and Nishiguchi *et al*[59-60] found that the increase of aqueous flare in patients with RP was attributed to the destruction of the blood-retinal barrier caused by inflammation in the eyes, and the increase of aqueous flare often led to a decline in visual function. Nevertheless, they failed to prove the relationship between them. Later, Fujiwara *et al*[61] confirmed that aqueous flare had been a more sensitive sign of intraocular inflammation, and a suitable marker for assessing the progression of RP. What they want to express is that an increase in aqueous flares means a decrease in BCVA and the MD value after eliminating confounding factors.

Systemic inflammation The appearance of high levels of serum high-sensitivity C-reactive protein (hs-CRP) is a risk factor for faster deterioration of the disease. As a representative of systemic inflammation, the alteration of hs-CRP is associated

with many eye conditions, such as AMD and diabetic retinopathy (DR)[62]. Similarly, during retinal degeneration in RP, the peripheral blood environment may be changed which proved in animal experiments[63]. In clinical trials, Murakami *et al*[64] evaluated the systemic inflammatory response of RP and the association between alteration in serum hs-CRP and central visual function in RP patients. Finally, they found that compared with the control group, the average serum hs-CRP of RP patients increased significantly (P=0.0119), and the deterioration of central visual function was faster in patients with higher levels of hs-CRP. However, hs-CRP measurements are susceptible to multiple confounding factors, such as lifestyle changes, smoking or not, and other systemic factors. These uncertain factors may reduce the credibility of the correlation between hs-CRP and visual function. Therefore, we should use the related conclusions with caution in clinical practice.

Oxidative Stress Factors On account of rod photoreceptors consuming the most oxygen, accounting for 95% of the total oxygen consumption of outer nuclear layer[65], and being directly exposed to light, oxidative stress will seriously affect the health of the retina. In addition, more and more evidences indicate that oxidative stress is involved in the pathogenesis of RP[66]. Therefore, reducing oxidative stress can prevent the apoptosis of photoreceptor cells and the progression of RP. Rezaie *et al*[67] studied the endogenous antioxidant machinery, such as phase 2 antioxidant enzymes, contributed to reduce oxidative stress in photoreceptor cells, whether *in vivo* or *in vitro* experiments, also concluded that the relationship between oxidative stress and disease progression cannot be ignored. However, the relationship between the endogenous antioxidant molecules and progression of the disease has not been supported by the evidence of clinical trials. Moreover, reduced ocular antioxidant status in patients with RP was confirmed by Martínez-Fernández de la Cámara *et al*[68]. Although, they concluded that the decline in the antioxidant capacity of the eye would lead to a corresponding reduction in the ability of the retina to process toxic oxygen intermediates in patients with RP, which further led to the deterioration of the disease, the relationship between the antioxidant status of the eye and the deterioration of visual function remained unclear.

From the research on relationship between oxidative stress and the progress of RP in recent years, the level of oxidative stress products in the eyes and the whole body shows conflicting results on the effects of diseases. Reactive oxygen species (ROS) is a common product in regular part of physical activity, so the organelles and molecules of the human body are always at risk of being oxidized by ROS. Once ROS is excessive, cell macromolecules such as nucleic acid and protein will be destroyed, and then cell function will be impaired or cells will transdifferentiate or even die[69]. When the balance between the normal production of ROS in the body and the antioxidant capacity is broken, the body's oxidative stress will increase. After oxidative stress increases, cell and molecular damage will occur. To prevent this, cells will mobilize their complex defense system to repair the damage they cause by neutralizing or catalyzing ROS and other oxidative stress products. For example, H_2O_2 is transformed into H_2O under the action of glutathione peroxidase (GPx), and glutathione (GSH) is transformed into disulfide form under the conversion of GPx. Therefore, the content of related catalytic enzymes or products in the body can affect the progression of the disease. Campochiaro and Mir[45] highlighted that number of carbonyl groups indicating oxidative damage increased in patients, and the ratio of reduced GSH to oxidized GSH decreased compared to the control in their aqueous humor. However, in the RP patients' peripheral blood, antioxidant and oxidant statuses have shown some conflicting results. In a cohort of 52 RP patients and 25 controls[70], lower activity of serum superoxide dismutase 3 (SOD3) was related to the serious retinal degeneration in patients, but other serum antioxidant/oxidant markers, including GPx, were confirmed no significant difference. There are few relevant clinical studies on the effect of oxidative stress products on the progression of RP, and most of them are now explored in animal models.

DISCUSSION

When we have reviewed the above risk factors for the progression of RP, these results should be used as much as possible to serve the clinic, and patients should be given better treatment and prevention guidance to prevent rapid disease progression or provide genetic counseling. However, how to reasonably take those risk factors into consideration requires us to further establish a reliable model for predicting disease progression for different individuals.

So far, genetic factors are the only identified risk factors associated with RP. However, only a few genes and their variants have been clearly elucidated for their influence on the development of RP, and can be well used to guide prenatal diagnosis or actively intervene in the condition. Further research is needed to better understand the genotype/phenotype relationship. Also, molecular diagnostic technology should be further developed, which is conducive to digging out more useful information and perfecting the gene lineage related to RP. The more genetic factors we know, the more stable the disease prediction model will be built.

For phenotypic risk factors, the combination of structural and functional measurements can provide a high level of sensitivity and reliability when measuring disease progression. They are well associated with RP, and in order to ensure the reproducible outcome measures, we recommend using multimodal imaging

to detect progression of RP for future clinical trials[71]. For predicting long-term progression in patients with RP, we may more likely to recommend functional measurements instead of structural ones. However, it is not ruled out that some scholars support the view that structural indicators such as EZ are superior to functional indicators such as MD or BCVA in monitoring disease progression[5].

With the improvement of molecular diagnostic technology, more and more inflammatory factors have been proved to be related to RP, and local inflammation and systemic inflammation can be combined to predict the progression of the disease. However, if the hospital does not have corresponding detection methods and advanced equipment to detect related inflammatory factors, such as the value of aqueous flare, macroscopic clinical manifestations still have access to predicting disease progression. Fujiwara *et al*[72] showed that high aqueous flare is an important risk factor for the formation of posterior subcapsular cataract (PSC), which suggests that inflammation may be involved in the pathogenesis of PSC formation in RP. Therefore, the conclusion of this study can be used to roughly judge the progression of RP by observing the formation of PSC under a slit lamp.

RP is a hereditary disease, in addition to the determination of genetic factors, there are few studies on demographic and environmental factors that affect the progress of RP, such as light exposure, ethnicity and comorbidity. Non-genetic biological factors, including oxidative stress, also control or promote disease progression. However, prospective studies to investigate the level of oxidative stress products and disease progression are limited. If these factors are determined to be related to the progression of RP in further studies, they will add new evidence to the clinical prediction of RP and contribute to the prevention of disease progression.

Up to now, there is no ideal predictive model to predict disease progression, or a predictive model with only a single risk factor. It requires more high-quality prospective studies to discover more reliable factors that predict disease progression, especially in the molecular mechanism of RP. Only then can we apply computer simulation to establish a mixed-effect model of the risk factors that affect the progression of RP. The ultimate goal is to serve the prevention and treatment of RP in the clinic.

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