

## Original Article

# A distinct form of retinitis pigmentosa with retinal vascular occlusion

Mingyang Wang<sup>1</sup>, Ningli Wang<sup>1</sup>, Xiaorong Li<sup>2</sup>, Guanglu Wang<sup>1</sup>

<sup>1</sup>Beijing Tongren Eye Center, Beijing Tongren Hospital Affiliated to Capital University of Medical Sciences, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing 100730, China; <sup>2</sup>The Eye Center of Tianjin Medical University, Tianjin 300070, China

Received June 9, 2017; Accepted March 22, 2018; Epub June 15, 2018; Published June 30, 2018

**Abstract:** Objective: To describe and analyze the clinical features and results of exome sequencing of a distinct form of retinitis pigmentosa (RP) associated with retinal vascular occlusion (RVO). Design: This case series was a retrospective study. Participants: 23 patients with RP/RVO during 1992-2015. Methods: Information obtained from medical records includes age, gender, clinical history, visual acuity, and results of investigations using the slit-lamp, indirect ophthalmoscope, fundus photography, optical coherence tomography, angiography, electroretinography (ERG) and visual evoked potentials (VEP). Exome sequencing was performed in 8 blood samples. Results: Both eyes were affected. The optic disc was pale in 25 eyes, pale-white in 20 and normal in 1. Retinal vessels were attenuated in all eyes. There were widespread retinal pigment epithelium (RPE) abnormalities, including pigment discoloration and pigmented spots; no 'bone spicules' were observed. There was no inflammation, exudation, hemorrhage, neovascularization or proliferative vitreoretinopathy. Dye filling of vessels (angiography) was minimal/absent in 22 eyes, extended 1-3 diameters from the disc in 12, reached the posterior pole in 8, and reached the periphery in 4. ERG revealed severe a- and b-wave attenuation in 13 cases. VEP recordings showed implicit time prolongation and reduced amplitude. In 2 cases, progression from an intermediate to an advanced stage took 3.5-4 years. Prognosis was poor. In the results of exome sequencing, we found the SNP related RP, which had been reported previously. Conclusion: RP with RVO may be a distinct form of RP.

**Keywords:** Choroidal vessel atrophy, optic atrophy, retinal pigment epithelium atrophy, retinal vessel occlusion, retinitis pigmentosa

## Introduction

Retinitis pigmentosa encompasses a group of inherited pigmentary retinopathies that affect approximately 1 in 4000 people [1-3]. Retinitis pigmentosa is characterized by the progressive degeneration of rod and cone photoreceptors and loss of retinal pigment epithelium (RPE) cells, eventually resulting in atrophy of retinal tissue [1-3]. Typically, patients with this disease initially experience night blindness (since degeneration occurs first in photoreceptor rods) followed sequentially by patchy losses of mid-peripheral vision, tunnel vision and eventually loss of central vision [4, 5]. The main fundus changes in patients with retinitis pigmentosa include a waxy-pale optic disc, attenuation of the retinal vessels, extensive retinal atrophy, areas of depigmentation and pigmen-

tary deposits (initially in the peripheral retina) that resemble bone spicules [4, 5]. Electroretinography (ERG) characteristically shows attenuation of a- and b-waves [5]. Currently, there are no known therapies that can stop or reverse the progression of the disease; hence, prognosis is poor.

In recent years, retinitis pigmentosa with progressive retinal vascular occlusion has been increasingly recognized in the clinical setting, but there have been few publications describing this uncommon presentation of the disease. In China, a few case reports have been published describing a small number of patients with 'primary bilateral vaso-obliterative optic neuroretinopathy', which was considered by various authors to be vascular occlusion of unknown cause [6-9]. However, the manifesta-

tions of the disorders described in these studies were consistent with those of retinitis pigmentosa, but with some unique features of vascular occlusion. Other than one report of a patient with retinitis pigmentosa and Usher syndrome who developed ischemic central retinal vein occlusion in one eye [10], there have been no international (i.e. non-Chinese) studies of retinitis pigmentosa with progressive retinal vascular occlusion. Respectful Dr. Donald Gass once pointed out that obliteration of the vessels was very unusual after receiving our material. The primary description of the clinical characteristics of patients with retinitis pigmentosa and progressive retinal vascular occlusion were published in Chinese Journal of Ophthalmology in 2005 [11]. The author also reported this point of view in the conference speech at the 116th Annual Meeting of the Japanese Ophthalmological Society in 2012 and found no related reports in Japan. The disease has not yet been reported out of China till now. Tongren Hospital is the largest ophthalmic center in China, and provides abundant opportunities to collect and study RP with RVO cases. This article describes the clinical features of retinitis pigmentosa with retinal vascular occlusion based on a retrospectively analyzed case series from 1992-2015, incorporates further analysis on exome sequencing, and thus improves the understanding of the main characteristics of this disease.

### Patients and methods

#### *Patients*

This case series was a retrospective analysis of patients with retinitis pigmentosa and retinal vascular occlusion examined at the Beijing Tongren Eye Center (Beijing, China) between 1992 and 2015. The study was approved by the ethics committee of Beijing Tongren Eye Center. Due to the retrospective nature of the analysis, informed consent from the study participants was deemed not to be required.

The inclusion criteria were: 1) clinical examination revealed fundus changes that were characteristic of retinitis pigmentosa, including a pale optic disc, retinal vessel attenuation, extensive retinal atrophy, areas of depigmentation and/or pigmentary deposits; 2) ERG demonstrated depression or extinguishment of a- and b-waves; and 3) fundus photography, fun-

us fluorescein angiography or indocyanine green angiography also provided evidence of retinal vascular occlusion. The patient was excluded from the analysis if any of the following was detected: 1) retinal hemorrhage; 2) retinal neovascularization; 3) vitreoretinal proliferation; 4) vitreous hemorrhage.

#### *Data collection*

The following clinical information was retrospectively collected from the patients' electronic records: age; gender; clinical history including presenting symptoms and disease duration (i.e. time from the initial occurrence of symptoms); visual acuity; and the results of clinical examinations using the slit-lamp, indirect ophthalmoscope, fundus photography, optical coherence tomography (OCT), fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), ERG and visual evoked potential (VEP) measurement.

#### *Follow-up*

Patients were followed-up every 3-6 months. Clinical examinations conducted at follow-up included visual acuity testing, slit-lamp examination, fundus photography and fluorescein angiography.

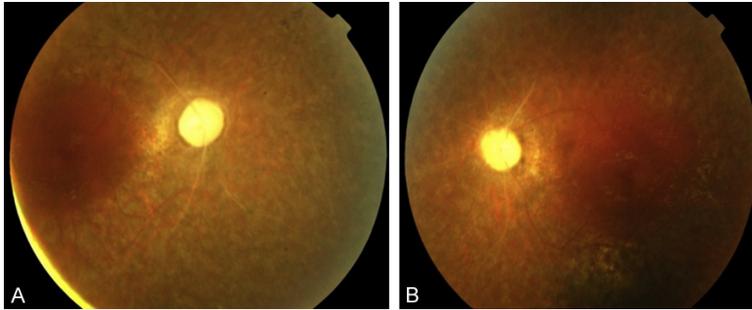
#### *Statistical analysis*

A descriptive statistical analysis was undertaken. Data were analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Continuous data are presented as the mean  $\pm$  standard deviation (SD), while count data are expressed as numbers and percentages.

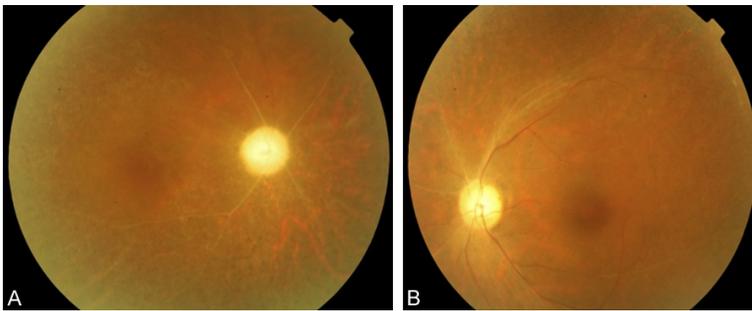
### Results

#### *Baseline clinical characteristics of the patients included in the study*

A total of 23 patients (12 males; 52.2%) were included in the final analysis. Patient age averaged  $49.96 \pm 15.80$  years and ranged from 6-70 years (<30 years, 2 cases; 30-40 years, 2 cases; 41-50 years, 7 cases; >50 years, 12 cases). Both eyes were affected in all patients. The presenting symptom in all cases was blurred vision in one or both eyes. The duration of the disease (from the time of the initial symptoms) ranged from 2 months to 10 years. There was no family history of retinitis pigmentosa or



**Figure 1.** Color photographs of the fundi in a 17-year-old male (case 9). A. Right eye. B. Left eye. In both eyes, the optic disc was very pale ('moon-like'), the retinal vessels were obliterated and there were widespread abnormalities of the retinal pigment epithelium, including pigment discoloration.



**Figure 2.** Color photographs of the fundi in a 53-year-old female (case 22). A. Right eye. The optic disc was very pale ('moon-like') and the retinal vessels were obliterated. B. Left eye. The optic disc was pale and the retinal vessels were attenuated.

history of aphthous ulcer or contact with poisons/toxins for any of the patients.

Visual acuity was determined to be  $\leq 0.05$  in 31 eyes (no light perception, 11 eyes; light perception, 9 eyes; hand motion, 4 eyes; finger counting, 2 eyes); 0.06-0.3 in 7 eyes; and  $>0.3$  in 8 eyes. No anterior segment inflammation or iris neovascularization were observed.

#### *Slit-lamp and fundus examinations*

Ocular tension was normal in all eyes. Cataracts were present in both eyes of 10 cases (43.5%). The optic disc color was pale in 25 eyes (54.3%), very pale ('moon-like') in 20 eyes (43.5%) and normal in 1 eye (2.2%). The retinal vessels in all eyes were attenuated, especially on the nasal side where there was tapering from a normal blood column in the periphery to no blood column at the optic disc. There were widespread abnormalities of the RPE, including pigment discoloration and the presence of tiny, pigmented spots; however, no typical pigmentary spots

resembling bone spicules were observed. There were no signs of inflammation, exudation, hemorrhage, neovascularization or proliferative vitreoretinopathy. Choroidal vessels were seen in advanced cases (**Figures 1, 2**).

#### *Angiography*

The fluorescence of the optic disc detected during angiography varied between patients and ranged from hypofluorescence in the early phase and faint dye staining in the later phase to a normal appearance. Vascular filling with dye was minimal or absent at the optic disc in 22 eyes (47.8%); extended 1-3 disc diameters from the disc in 12 eyes (26.1%); extended to the posterior pole in 8 eyes (17.4%); and reached the equator or periphery in 4 eyes (8.7%; **Table 1**). In all eyes, fluorescein staining of the peripheral retina had a 'salt-and-pepper' appearance; in addition, 16 eyes also showed 'salt-and-pepper' staining of the macular area. Vascular staining with dye was observed in 4 eyes. ICGA showed that the choroidal vessels were attenuated, choroidal fluorescence was faint and dye regression was rapid. Pigmented spots were observed to block the fluorescence. Vascular occlusion was also seen, similar to that detected by FFA.

#### *OCT, visual field examination and electrophysiological investigation*

OCT demonstrated thinning of both the neurosensory retina and RPE layer and flattening of the macular curve (indicating disappearance of the macular fovea). Visual field examination showed concentric contraction to 10-20° in 13 cases. ERG revealed complete or severe attenuation of a- and b-waves in 13 cases. VEP recordings showed a prolonged implicit time and a greatly reduced or zero amplitude. Transcranial Doppler ultrasound investigations were normal in 5 cases. Color Doppler imaging in 10 cases showed abnormal central retinal artery

## RP with retinal vascular occlusion

**Table 1.** Clinical features of the patients with retinitis pigmentosa and vascular occlusion

Case	Sex	Age	Visual acuity		Anterior segment		Disc color		Retinal vessel	
			RE	LE	RE	LE	RE	LE	RE	LE
1	M	43	LP	0.02			++	+	1	2
2	M	66	LP	0.6	Cat	Cat	++	+	1	3
3	F	59	HM	HM	Cat	Cat	+	++	2	2
4	F	63	NLP	HM	Cat	Cat	++	+	1	2
5	F	63	0.3	0.2	Cat	Cat	+	+	3	3
6	M	35	0.8	LP			+	++	1	1
7	M	70	NLP	0.3	Cat	Cat	++	+	1	2
8	F	42	0.5	0.8			+	+	3	4
9	M	17	LP	LP			++	++	1	1
10	F	60	0.02	NLP	Cat	Cat	+	++	2	1
11	F	44	1.2	NLP			N	++	4	1
12	M	65	FC	HM	Cat	Cat	+	++	2	1
13	F	64	0.1	0.1	Cat	Cat	+	+	2	3
14	M	6	LP	LP			++	+	1	1
15	M	57	0.6	NLP	Cat	Cat	+	++	4	1
16	M	54	0.01	NLP			+	++	3	1
17	M	47	NLP	0.1			++	+	1	2
18	F	62	NLP	NLP	Cat	Cat	++	++	1	1
19	M	50	NLP	LP			++	+	1	2
20	F	46	FC	0.8			++	+	1	4
21	M	49	0.04	NLP			+	++	2	1
22	F	53	0.07	0.4			+	+	1	3
23	F	34	0.3	0.4			+	+	2	3

Abbreviations: Cat, cataract; F, female; FC, finger counting; HM, hand motion; LE, left eye; LP, light perception; M, male; NLP, no light perception; RE, right eye. Key to disc color observations: ++, pale-white optic disc ('moon-like'); +, pale optic disc; N, normal optic disc. Key to retinal vessel observations: 1, vessel dye barely seen or no vessel dye on disc; 2, vessel dye extends 1-3 disc diameters from the disc; 3, vessel dye extends to the posterior pole; 4, vessel dye extends to the equator or periphery.

blood flow with increased resistance and normal blood flow in the ophthalmic artery.

### Follow-up

In 2 cases, the progression of retinitis pigmentosa from an intermediate to an advanced stage took 3.5-4 years (**Figures 3, 4**). The prognosis was poor. At the time this study was undertaken, 26/46 eyes (56.5%) were blind and 12/46 (26.1%) had low visual acuity. In the absence of an effective therapy, all eyes eventually went blind.

### Genetic screening

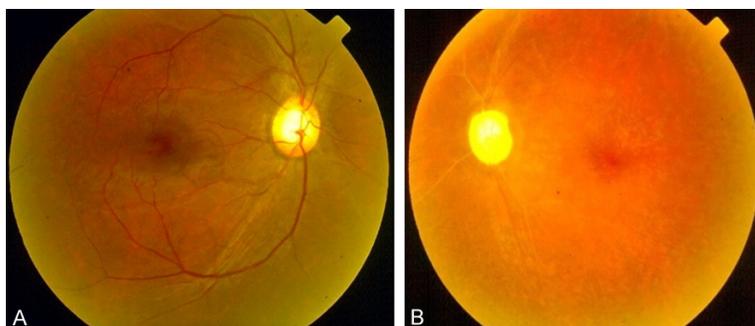
Genetic screening by exome sequencing was performed in 6 cases and additionally in the parents of case 23. Mutations were found in genes known to be related to retinitis pigmentosa (such as RP1 and USH2A) as well as in

unknown genes. The missense variants of RP1 gene were found in case 22, the father of 23 and 23 herself. The missense variants of USH2A gene were found in case 1, 2 and 23. KEGG pathway analysis indicated that the mutated genes were involved in several pathways, including those relating to apoptosis, vascular endothelial growth factor and retinol (**Table 2**).

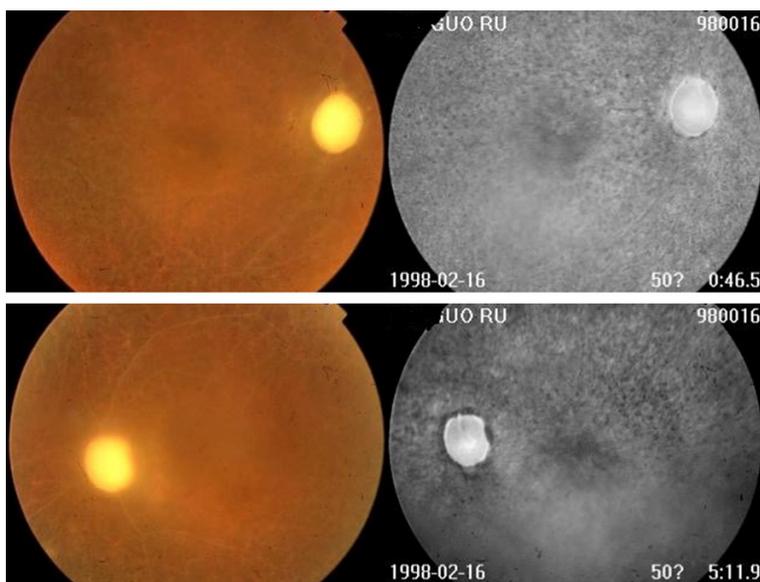
### Discussion

The present retrospective case series describes 23 patients which accord with the diagnosis of retinitis pigmentosa with retinal vascular occlusion. To the best of our knowledge, this particular disorder has not been reported outside of China. Although one international study described a single patient with retinitis pigmentosa and Usher syndrome who developed ischemic central retinal vein occlusion in one eye

## RP with retinal vascular occlusion



**Figure 3.** Color photographs of the fundi in a 35-year-old male (case 6) at presentation. A. Right eye. Visual acuity was 20/25. The disc was mildly pale. The arteries showed narrowing, and mild pigmentary changes were evident in the temporal fundus (visible at the temporal edge of this photograph). B. Left eye. Visual acuity was 'light perception'. The disc was markedly pale. The vessels were greatly attenuated and occlusion of the arteries was evident. There were diffuse pigment abnormalities throughout the posterior pole.



**Figure 4.** Color photographs and fluorescein angiograms of the fundi in a 35-year-old male (case 6) 3.5 years after presentation. Visual acuity in both eyes was 'light perception'. Upper left: Color photograph of the right eye. There was marked disc pallor, diffuse mild abnormalities of the retinal pigment epithelium and vessel obliteration, similar to that observed in the left eye at the initial presentation. Upper right: Fluorescein angiogram of the right eye. No vascular filling with dye was observed. Lower left: Color photograph of the left eye. Disc pallor, diffuse abnormalities of the retinal pigment epithelium and vessel obliteration was seen. Lower right: Fluorescein angiogram of the left eye, showing no vascular filling with dye.

[10], there have been no reports outside China of bilateral retinal vascular occlusion in patients with retinitis pigmentosa. The clinical features of this disease include an insidious onset, slow progression to blindness, a middle-age predilection (the average age of our patients was ~50 years), the involvement of both eyes with

asymmetrical involvement in the early stages, a history of nyctalopia and ocular manifestations characteristic of both retinitis pigmentosa and retinal vascular occlusion. The patients described in the study had clinical manifestations consistent with retinitis pigmentosa (optic atrophy, retinal vessel attenuation, RPE atrophy with depigmentation and/or fine pigment spots, and almost complete a- and b-wave extinction on ERG) as well as additional unique features, including total or near-total vascular obliteration, marked optic atrophy in the later stages and choroidal vessel abnormalities. It is important to note that visual loss was more rapid in this form of retinitis pigmentosa than in the typical form.

The pathogenesis of retinitis pigmentosa combined with retinal vascular occlusion remains unknown. One possibility is that the disorder may be caused by vascular inflammation, such as the disease which is associated with Behçet's disease. The age range of these patients is wide. The lesions are asymmetrical in both eyes, and vascular leakage could be present in some cases. However, in the present study, there were no signs of inflammation in the anterior or posterior segments, and no instances of retinal hemorrhage, exudation, neovascularization, proliferation, vitreous hemorrhage, aneurysm at the optic disk or at an artery, or apthous ulcer. This would indicate that vascular inflammatory disease was not the cause of retinitis pigmentosa and retinal vascular occlusion in our cohort data. Some authors [6, 7] have suggested that the primary pathogenetic site may be the vascular system and that this in turn leads to neuroretinopathy, i.e. the

## RP with retinal vascular occlusion

**Table 2.** The results of secondary screening (removing low quality sites) have been reported in the RP related genes

Chr	Position	dbSNP ID	In # of Samples	Description
1	216172380	rs10864219	6	Usher syndrome 2A (autosomal recessive, mild)
1	216219781	rs6657250, COSM146769	5	Usher syndrome 2A (autosomal recessive, mild)
3	100963154	rs571391	8	Interphotoreceptor matrix proteoglycan 2
6	65622463	rs9294631	6	Eyes shut homolog (Drosophila)
8	55539057	rs444772	3	Retinitis pigmentosa 1 (autosomal dominant)
X	38144822	rs12688514	2	Retinitis pigmentosa GTPase regulator
X	38144856	rs12687163	3	Retinitis pigmentosa GTPase regulator
X	38147170	rs1801688	2	Retinitis pigmentosa GTPase regulator
X	38156677	rs1801687	2	Retinitis pigmentosa GTPase regulator

RPE derangement was secondary to vascular changes. We agree that vascular changes are likely to be an important factor in the disease. We also found that RPE atrophy was already evident in cases where the retinal vessels were not occluded. Furthermore, vascular occlusion did not completely parallel the distribution of the RPE atrophic area, and there were cases in which vascular filling with dye was evident despite the ERG b-wave being dramatically attenuated or absent. These observations cannot be explained by vascular changes alone but could be accounted for by dystrophy of the retinal outer segment and choroid (including the photoreceptors, RPE and choriocapillaris). The major characteristics of this disease were optic atrophy, retinal vessels attenuation or obliteration, wide spread RPE depigmentation and/or fine pigment spots, total or nearly total ERG a- and b-wave extinction. As these findings were in accordance with the characteristics of RP, we believe that this type of disease is probably a form of tapeto-retinal dystrophy; however, it also differs from typical retinitis pigmentosa in four ways. First, there was progressive vascular occlusion. The vessels initially became attenuated and occluded from the periphery to the posterior pole before finally becoming totally occluded; this occurred at different times to different patients after the disease onset. FFA angiograms demonstrated that, eventually, only a small residual section of the disc showed vascular filling with dye, or there was complete absence of vascular filling with dye at the disc; typically, these changes are not seen in advanced retinitis pigmentosa. Second, there was striking optic atrophy, with the optic disc changing from an initial pale color to almost white-quite different from that seen in typical advanced retinitis pigmentosa. Moreover, mea-

surement of VEP showed that optic nerve function was seriously compromised. Third, RPE atrophy was prominent and occurred with or without the presence of fine pigmented spots; there were no deposits resembling bone spicules. Thus, some cases resembled retinitis pigmentosa sine pigmenti. But retinitis pigmentosa sine pigmenti is without the above specific characteristics presented in our cases. Fourth, the disease seemed to develop more rapidly than typical retinitis pigmentosa. In 2 cases, the progression from an intermediate to an advanced stage took 3.5-4 years. It is recognized that retinitis pigmentosa has many phenotypes, and the disorder described in this study may be one of those. However, in order to be recognized as a distinct entity, it would be necessary to establish that this form of retinitis pigmentosa has its own unique set of gene mutations. Dr. Donald Gass once via mail considered that vascular change of the disease was unusual after receiving our material and pointed out that RP has many phenotypes. It's unlikely to be a new title unless it has its own gene changes. This disease was not described in his books, neither in Heckenlively's papers. This point of view was once selected as the conference speech in the 116th annual meeting of the Japanese Ophthalmological and international meeting in 2012, no related reports existed in Japan when conference communicated.

From a clinical perspective, it will be important to differentiate this form of retinitis pigmentosa from bilateral progressive occlusive retinal vasculitis [12, 13], Behçet's disease or idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN) syndrome [14, 15]. The latter disease presents with aneurysms at the optic disk or at

an artery, exudative retinopathy, uveitis, vascular occlusion that develops from the periphery to the posterior pole, and sometimes neovascularization on the disc and/or iris, proliferative vitreoretinopathy and vitreous hemorrhage. The prognosis of IRVAN syndrome is notably better than that of the disorder described in this study, since IRVAN syndrome is sensitive to laser photocoagulation and vision can be saved if the disease is treated early. Behçet's disease presents with both anterior and posterior inflammation, relapsing aphthous ulcer, erythema nodosum, hypopyon in the anterior chamber and vascular inflammation and occlusion in some advanced cases; these features can differentiate Behçet's disease from the disorder presented in this case series.

Exome sequencing [16-26] was performed in 8 blood samples (6 from patients, and 2 from 1 patient's parents). We tried to find the potential sites and pathogenic genes considering the real clinical experience [27-37]. Single Nucleotide Polymorphism (SNP) sites related RP were found in the results of exome sequencing. Mutations were found in genes known to be related to retinitis pigmentosa (such as RP1 and USH2A) as well as in unknown genes. For example the missense variants of RP1 gene were found in case 22. It is still under investigation that whether the sites have functional relation with RP. Many unknown gene mutation sites which lead to amino acid modified were tried to explain the reason of vascular occlusion. Gene annotation found that these sites were related to apoptosis, neurodegeneration, inhibited proliferation.

This study has some limitations. First, this was a retrospective analysis, so it cannot be excluded that there was selection or/and reporting bias. Second, since the analysis was descriptive in nature, it is not possible to draw definitive conclusions. Third, not all patients were followed-up closely from the time of symptom onset, hence a detailed understanding of how the disease develops and progresses is lacking. Fourth, exome sequencing was only performed in some patients, prohibiting a detailed analysis of the genetic mutations that may underlie this disorder. Additional studies with larger cohorts, longer follow-up, and greater attention to genetic analyses of the cases and their families may disclose the precise nature of this disease.

In conclusion, this study described the clinical manifestation and exome sequencing features of retinitis pigmentosa associated with retinal vascular occlusion, and supported the perspective that it probably belonged to a kind of tapeto-retinal dystrophy, and vascular progressive occlusion may be one of RP phenotypes. It needs better follow up and family study to answer the question.

### Acknowledgements

This paper is dedicated respectfully to Dr. Donald Gass and Dr. Guanglu Wang, who have both passed away. Dr. Donald Gass once helped differentiate this type of retinitis pigmentosa and encouraged us to publish these innovations. Dr. Guanglu Wang, the father of Dr. Mingyang Wang, Member of FC Cordes Eye Society of UCSF, paid ardent expectations to this paper when he was alive. DR. A.R. Irvine and J. Duncan (UCSF) assisted in critiquing and preparing this paper for publication.

### Disclosure of conflict of interest

None.

### Abbreviations

ERG, electroretinography; FFA, fundus fluorescein angiography; ICGA, indocyanine green angiography; IRVAN, idiopathic retinal vasculitis, aneurysms and neuroretinitis; OCT, optical coherence tomography; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; RVO, retinal vascular occlusion; SD, standard deviation; VEP, visual evoked potentials.

**Address correspondence to:** Dr. Mingyang Wang, Beijing Tongren Eye Center, Beijing Tongren Hospital Affiliated to Capital University of Medical Sciences, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing 100730, China. Tel: +86-15620-930619; E-mail: continent23@126.com

### References

- [1] Rivolta C, Sharon D, DeAngelis MM, Dryja TP. Retinitis pigmentosa and allied diseases: numerous diseases, genes, and inheritance patterns. *Hum Mol Genet* 2002; 11: 1219-27.
- [2] Hu DN. Genetic aspects of retinitis pigmentosa in China. *Am J Med Genet* 1982; 12: 51-6.
- [3] Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet* 2006; 368: 1795-809.

- [4] Ueda-Consolvo T, Fuchizawa C, Otsuka M, Nakagawa T, Hayashi A. Analysis of retinal vessels in eyes with retinitis pigmentosa by retinal oximeter. *Acta Ophthalmol* 2015; 93: e446-50.
- [5] Hamel C. Retinitis pigmentosa. *Orphanet J Rare Dis* 2006; 1: 40.
- [6] Qiao R. Primary bilateral vessel-obliterative neuro-retinopathy (2 cases). *Chinese Journal of Ocular Fundus Diseases* 1989; 5: 172-3.
- [7] Chen XJ, Qin L, Wei SH. Primary bilateral vessel-obliterative neuro-retinopathy: one case report. *Chinese Journal of Traditional Chinese Ophthalmology* 1996; 5: 103.
- [8] Liu GH. Primary bilateral vessel-obliterative neuro-retinopathy: one case report. *Journal of Da Lian Medical University* 1996; 18: 298.
- [9] Mao AL, Zhang ML. Primary bilateral vessel-obliterative neuro-retinopathy: two cases report. *Chinese Journal of Practical Ophthalmology* 2005; 23: 1349-50.
- [10] Paxhia MJ, Ting TD, Fekrat S. Ischemic central retinal vein occlusion and retinitis pigmentosa: lower risk of neovascularization? *Retina* 2001; 21: 179-80.
- [11] Wang GL, Lu N, Zhang F, Peng XY, Li Y, Wang MY. The characteristics of retinitis pigmentosa with retinal vascular occlusion. *Chinese Journal of Ophthalmology* 2005; 41: 414-8.
- [12] Qi Y, Wang G. Bilateral progressive obliterative vasculitis (IRVAN syndrome). *Chinese Journal of Ophthalmology* 1994; 30: 294-6.
- [13] Ohsaka K. Obliterative retinal vasculitis with extreme nonperfusion in the periphery in a child. *Japanese Journal of Clinical Ophthalmology* 1988; 42: 211-4.
- [14] Chang TS, Aylward GW, Davis JL, Mieler WF, Oliver GL, Maberley AL, Gass JD. Idiopathic retinal vasculitis, aneurysms, and neuro-retinitis. Retinal vasculitis study. *Ophthalmology* 1995; 102: 1089-97.
- [15] Wang G, Lu N, Wang M. Clinical feature and treatment of IRVAN syndrome. *Clinical Research* 2006; 24: 191-4.
- [16] Bonnefond A, Durand E, Sand O, De Graeve F, Gallina S, Busiah K, Lobbens S, Simon A, Bellanné-Chantelot C, Létourneau L, Scharfmann R, Delplanque J, Sladek R, Polak M, Vaxillaire M, Froguel P. Molecular diagnosis of neonatal diabetes mellitus using next-generation sequencing of the whole exome. *PLoS One* 2010; 5: e13630.
- [17] Montenegro G, Powell E, Huang J, Speziani F, Edwards YJ, Beecham G, Hulme W, Siskind C, Vance J, Shy M, Züchner S. Exome sequencing allows for rapid gene identification in a charcot-marie-tooth family. *Ann Neurol* 2011; 69: 464-470.
- [18] Biesecker LG. Exome sequencing makes medical genomics a reality. *Nat Genet* 2010; 42: 13-14.
- [19] Lee W, Jiang Z, Liu J, Haverty PM, Guan Y, Stinson J, Yue P, Zhang Y, Pant KP, Bhatt D, Ha C, Johnson S, Kennemer MI, Mohan S, Nazarenko I, Watanabe C, Sparks AB, Shames DS, Gentleman R, de Sauvage FJ, Stern H, Pandita A, Ballinger DG, Drmanac R, Modrusan Z, Seshagiri S, Zhang Z. The mutation spectrum revealed by paired genome sequences from a lung cancer patient. *Nature* 2010; 465: 473-477.
- [20] Saarinen S, Aavikko M, Aittomäki K, Launonen V, Lehtonen R, Franssila K, Lehtonen HJ, Kaasinen E, Broderick P, Tarkkanen J, Bain BJ, Bauduer F, Ünal A, Swerdlow AJ, Cooke R, Mäkinen MJ, Houlston R, Vahteristo P, Aaltonen LA. Exome sequencing reveals germline NPAT mutation as a candidate risk factor for Hodgkin lymphoma. *Blood* 2011; 118: 493-8.
- [21] Wei X, Walia V, Lin JC, Teer JK, Prickett TD, Gartner J, Davis S; NISC Comparative Sequencing Program, Stemke-Hale K, Davies MA, Gershenwald JE, Robinson W, Robinson S, Rosenberg SA, Samuels Y. Exome sequencing identifies GRIN2A as frequently mutated in melanoma. *Nat Genet* 2011; 43: 442-446.
- [22] Ding L, Ellis MJ, Li S, Larson DE, Chen K, Wallis JW, Harris CC, McLellan MD, Fulton RS, Fulton LL, Abbott RM, Hoog J, Dooling DJ, Koboldt DC, Schmidt H, Kalicki J, Zhang Q, Chen L, Lin L, Wendl MC, McMichael JF, Magrini VJ, Cook L, McGrath SD, Vickery TL, Appelbaum E, Deschryver K, Davies S, Guintoli T, Lin L, Crowder R, Tao Y, Snider JE, Smith SM, Dukes AF, Sanderson GE, Pohl CS, Delehaunty KD, Fronick CC, Pape KA, Reed JS, Robinson JS, Hodges JS, Schierding W, Dees ND, Shen D, Locke DP, Wiechert ME, Eldred JM, Peck JB, Oberkfell BJ, Lolofie JT, Du F, Hawkins AE, O'Laughlin MD, Bernard KE, Cunningham M, Elliott G, Mason MD, Thompson DM Jr, Ivanovich JL, Goodfellow PJ, Perou CM, Weinstock GM, Aft R, Watson M, Ley TJ, Wilson RK, Mardis ER. Genome remodelling in a basal-like breast cancer metastasis and xenograft. *Nature* 2010; 464: 999-1005.
- [23] Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, Boisson B, Picard C, Dewell S, Zhao C, Jouanguy E, Feske S, Abel L, Casanova JL. Whole-exome sequencing based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. *J Exp Med* 2010; 207: 2307-2312.
- [24] Yan XJ, Xu J, Gu ZH, Pan CM, Lu G, Shen Y, Shi JY, Zhu YM, Tang L, Zhang XW, Liang WX, Mi JQ, Song HD, Li KQ, Chen Z, Chen SJ. Exome sequencing identifies somatic mutations of DNA Methyltransferase gene DNMT3A in acute monocytic leukemia. *Nat Genet* 2011; 43: 309-315.
- [25] Choi M, Scholl UI, Ji WZ, Liu T, Tikhonova IR, Zumbo P, Nayir A, Bakkaloğlu A, Ozen S, Sanjad

- S, Nelson-Williams C, Farhi A, Mane S, Lifton RP. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc Natl Acad Sci U S A* 2009; 106: 19096-19101.
- [26] Worthey EA, Mayer AN, Syverson GD, Helbling D, Bonacci BB, Decker B, Serpe JM, Dasu T, Tschannen MR, Veith RL, Basehore MJ, Broeckel U, Tomita-Mitchell A, Arca MJ, Casper JT, Margolis DA, Bick DP, Hessner MJ, Routes JM, Verbsky JW, Jacob HJ, Dimmock DP. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet Med* 2011; 13: 255-262.
- [27] McClellan J, King MC. Genetic heterogeneity in human disease. *Cell* 2010; 141: 210-217.
- [28] Biesecker LG. Exome sequencing makes medical genomics a reality. *Nat Genet* 2010; 42: 13-14.
- [29] Gilissen C, Arts HH, Hoischen A, Spruijt L, Mans DA, Arts P, van Lier B, Steehouwer M, van Reeuwijk J, Kant SG, Roepman R, Knoers NV, Veltman JA, Brunner HG. Exome sequencing identifies WDR35 variants involved in Sensen-brenner syndrome. *Am J Hum Genet* 2010; 87: 418-423.
- [30] Lalonde E, Albrecht S, Ha KCH, Jacob K, Bolduc N, Polychronakos C, Dechelotte P, Majewski J, Jabado N. Unexpected allelic heterogeneity and spectrum of mutations in fowler syndrome revealed by next-generation exome sequencing. *Hum Mutat* 2010; 31: 918-923.
- [31] Pierce SB, Walsh T, Chisholm KM, Lee MK, Thornton AM, Fiumara A, Opitz JM, Levy-Lahad E, Klevit RE, King MC. Mutations in the DBP deficiency protein HSD17B4 cause ovarian dysgenesis, hearingloss, and ataxia of Perrault syndrome. *Am J Hum Genet* 2010; 87: 282-288.
- [32] Simpson MA, Irving MD, Asilmaz E, Gray MJ, Dafou D, Elmslie FV, Mansour S, Holder SE, Brain CE, Burton BK, Kim KH, Pauli RM, Aftimos S, Stewart H, Kim CA, Holder-Espinasse M, Robertson SP, Drake WM, Trembath RC. Mutations in NOTCH2 cause Hajdu-cheny syndrome, a disorder of severe and progressive bone loss. *Nat Genet* 2011; 43: 303-305.
- [33] Becker J, Semler O, Gilissen C, Li Y, Bolz HJ, Giunta C, Bergmann C, Rohrbach M, Koerber F, Zimmermann K, de Vries P, Wirth B, Schoenau E, Wollnik B, Veltman JA, Hoischen A, Netzer C. Exome sequencing identifies truncating mutations in human SERPINFI in autosomal-recessive osteogenesis imperfecta. *Am J Hum Gene* 2011; 88: 362-371.
- [34] Haack TB, Danhauser K, Haberberger B, Hoser J, Strecker V, Boehm D, Uziel G, Lamantea E, Invernizzi F, Poulton J, Rolinski B, Iuso A, Biskup S, Schmidt T, Mewes HW, Wittig I, Meitinger T, Zeviani M, Prokisch H. Exome sequencing identifies ACAD9 mutations as a cause of complex I deficiency. *Nat Genet* 2010; 42: 1131-1134.
- [35] Ng SB, Buckingham, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, Shendure J, Bamshad MJ. Exome sequencing identifies the cause of a mendelian disorder. *Nat Genet* 2009; 42: 30-35.
- [36] Johnson JO, Gibbs JR, Van Maldergem L, Houlden H, Singleton AB. Exome sequencing in brown-vialetto-van laere syndrome. *Am J Hum Genet* 2010; 87: 567-569.
- [37] Krawitz PM, Schweiger MR, Rodelsperger C, Marcelis C, Kölsch U, Meisel C, Stephani F, Kinoshita T, Murakami Y, Bauer S, Isau M, Fischer A, Dahl A, Kerick M, Hecht J, Köhler S, Jäger M, Grünhagen J, de Condor BJ, Doelken S, Brunner HG, Meinecke P, Passarge E, Thompson MD, Cole DE, Horn D, Roscioli T, Mundlos S, Robinson PN. Identity by descent filtering of exome sequence data identifies PIGV mutations in hyperphosphatasia mental retardation syndrome. *Nat Genet* 2010; 42: 827-829.