Case Report

Fundus albipunctatus: A Case Report in Thailand and a Review of the Literature

Ngamkae Ruangvaravate MD*, Atiporn Thuangtong MD*, Nacha Chanvarapha MSc*

* Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Fundus albipunctatus (FA) is classified as a congenital stationary form of night blindness with classic fundus and electrophysiologic findings. Characteristic fundoscopy reveals numerous whitish-yellow spots located in the retinal pigment epithelium that extend from the posterior pole to the periphery. Electroretinographic (ERG) recordings are very distinctive in patients with FA. The amplitude of scotopic (rod) ERG is significantly reduced when recorded after conventional dark adaptation, but it becomes larger and comes to normal range after prolonged dark adaptation (more than two hours). FA has been attributed to mutation in the RDH5 gene, which encodes 11-cis retinol dehydrogenase, an enzyme that is essential for the regeneration of visual pigments in the retina. To date, at least 100 patients with FA and 44 mutations in the RDH5 gene have been reported worldwide. FA is a rare disease that is inherited as an autosomal recessive trait. Here, we report the first case of FA in Thailand and a review of the literature.

Keywords: *Fundas albipunctatus, FA, Whitish-yellow spots, ERG*

J Med Assoc Thai 2017; 100 (11): 1241-6
Website: http://www.jmatonline.com

Fundus albipunctatus (FA) is a rare autosomal recessive form of congenital stationary night blindness that has characteristic fundus and electrophysiologic findings. Fundus findings reveal numerous whitish-yellow spots deep in the retina, expanding from the posterior pole (outer macular area) to the periphery[1]. The deposits are localized between the outer limiting membrane and the outer aspect of the retinal pigment epithelium (RPE), as observed on optical coherence tomography (OCT)[2-4]. Electroretinographic (ERG) findings are very distinctive in patients with FA. Standard full-field ERG shows depressed rod responses, which may recover after prolonged dark adaptation for two to three hours[5,6]. The amplitude of the scotopic ERG recording is significantly reduced when recorded after 20 to 30 minutes of dark adaptation, but it becomes larger and comes to near-normal or normal range after prolonged dark adaptation[7]. Carr et al reported that the basic mechanism in the pathogenesis of FA is delayed regeneration of rod visual pigments[8].

Most cases of FA are caused by mutations in the retinal dehydrogenase 5 (RDH5) gene, which encodes 11-cis retinol dehydrogenase (11-cis-RDH)[9,10]. The 11-cis-RDH is expressed predominantly in the RPE and is known to be essential for regeneration of visual pigments in the retina[7].

Patients with FA have night blindness that begins in childhood and they usually complain of a delay in dark adaptation after exposure to bright light. The clinical course of FA is mostly stationary with normal visual acuity and color perception. As a result, FA patients usually have a normal daily life and they normally do not consult an ophthalmologist for eye examination. In this report, the authors present the first reported case of FA in Thailand along with a review of the literatures.

Case Report

A 39-year-old woman with hyperthyroidism diagnosed three years earlier and was being treated at the Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Siriraj Hospital is the Thailand's largest national tertiary referral center. The written informed consent was obtained from our patient before proceeding with this report.

The patient was referred for an ophthalmology consult to evaluate for thyroid ophthalmopathy. She presented with proptosis of her left eye with lid lag and lid retraction. In contrast, her right eye appeared normal. Computerized tomography (CT) of the orbit revealed mild enlargement of the inferior and lateral rectus muscles of the left extraocular muscles. She complained of periodic dry eye irritation relieved by

Correspondence to:
Ruangvaravate N. Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-2-4198033, Fax: +66-2-4111906
E-mail: ngamkae1@gmail.com

tear supplementation. Her visual acuity was 20/30 in both eyes and the intraocular pressure in her left and right eye was 18 and 16 mmHg, respectively. The anterior segment was normal, except for mild punctate epithelial erosion on the left eye caused by thyroid ophthalmopathy. Fundoscopy revealed numerous whitish-yellow spots in the perimacular region and throughout the peripheral retina in both eyes (Fig. 1). The optic disc and retinal vessels were normal. After evaluating the results of her fundoscopy, which revealed flecked retinal disease, she was asked to provide details about her vision in a dark condition.

Our patient reported having mild night visual impairment since she was young, but her impairment did not progress and did not disturb her normal functions of daily living. Her color vision test was normal and her visual field was unremarkable in both eyes. Full-field ERG recordings were performed according to standards and criteria set forth by the International Society for Clinical Electrophysiology of Vision. Using a Nicolet Viking select master software v7.1 (Nicolet Biomedical Incorporated, Pleasanton, CA, USA) with skin electrodes (Ag/AgCl). ERG revealed normal cone responses (photopic and flicker ERGs) and mild decreased amplitude of b wave on mesopic ERG. The b wave amplitude on scotopic ERG was significantly reduced when recorded after conventional dark adaptation (20 minutes), but it became larger and came to within normal range after prolonged dark adaptation (90 minutes) (Fig. 2). These ERG findings indicated delayed regeneration of rod visual pigments during conventional dark adaptation testing, but after two to three hours of dark adaptation, rod sensitivity improved to normal levels. Accordingly, the symptoms and findings of stationary night vision impairment, numerous whitish-yellow retinal lesions found throughout the retina (except the fovea), and ERGs showing delayed regeneration of rod visual pigments facilitated the diagnosis of FA in this patient.

ERG findings in FA patients are very distinctive and telling. Our patient is single, unmarried, and no other member of her immediate or extended family has similar symptoms of impaired night vision. The investigators recommended that she submit to a blood test and agree to genetic study to evaluate for gene mutations. However, and for reasons that she did not disclose, our patient decided against genetic analysis. Even without confirmation by genetic study for RDH5 mutation, the diagnosis of FA was made based on characteristic fundus and distinctive ERG findings. Based on our review of the literature, this is the first reported case of FA in Thailand.

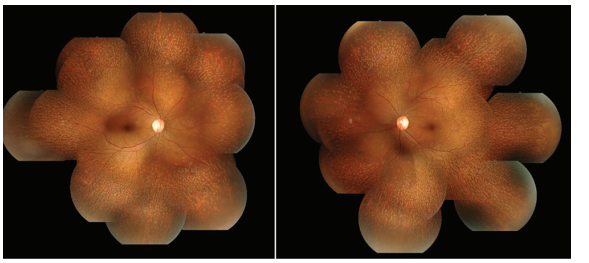

Fig. 1 Montage color fundus photographs demonstrating numerous whitish-yellow spots in the midperipheral and peripheral retina of both eyes.

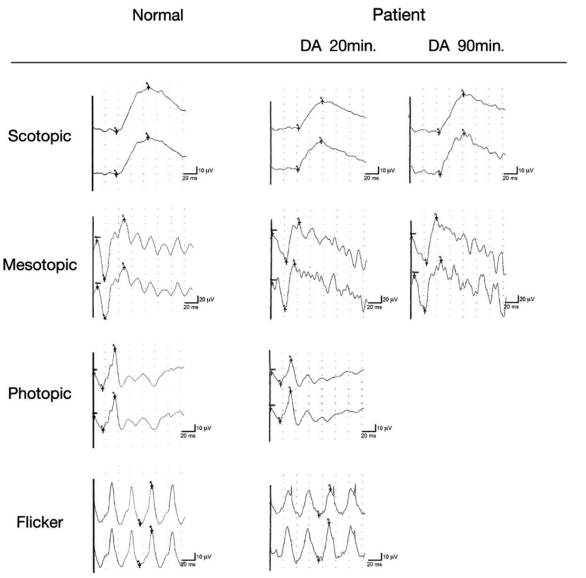

Fig. 2 Electoretinograms demonstrated a reduction of b waves in scotopic responses when recorded after dark adaptation (DA) 20 minutes. Then, b wave amplitudes became larger to normal range after prolong DA 90 minutes (the upper and lower waves of each response came from the recording of right and left eye, respectively).

Discussion

FA (OMIM: 136880; Orphanet: 227796) is a rare form of congenital stationary night blindness characterized by striking fundus and electrophysiological findings. FA follows an autosomal recessive pattern of inheritance[11]. FA patients normally have night vision impairment since childhood and delayed dark adaptation after exposure to bright light. The symptoms of defective dark adaptation may not be noticeable to affected persons, because their condition is their known normal. No abnormalities in visual

field or visual acuity are normally detected unless a dim stimulus is applied. Dim stimulus can cause a worsening of visual acuity and visual field constriction. FA was originally and widely considered to be a stationary type of night blindness. However, recent studies have shown that the disease is not stationary, with those studies finding that deterioration of cone visual function and cone dystrophy may develop[1,7,12]. Niwa et al reported that approximately 38% of Japanese patients with FA have extensive dysfunction of the cone system throughout the retina[7]. Several elderly patients with FA were diagnosed with cone dysfunction, which led to an assumption that FA may progress with age[2]. Another study in a large Caucasian FA population found cone dysfunction in 67% of their subjects[3]. These findings may indicate that cone dysfunction should be recognized as a major phenotypic finding in FA. It was also reported that patients with FA that do not present with macular lesions can have FA-associated cone dysfunction[7].

Fundoscopy findings in FA are characterized by abundant small whitish-yellow spots that are positioned throughout the retina (except the fovea), without vascular or optic nerve abnormalities. FA belongs to a heterogenous group of genetically determined flecked retina syndromes. Flecked retina syndromes include FA, retinitis punctate albescens (RPA), fundus flavimaculatus (Stargardt disease), familial drusen, and fleck retina of Kandori[13]. FA has to be distinguished from RPA, which is a variant of retinitis pigmentosa, in which the fundus shows yellow-white dots, but has constricted vessels and severely depressed ERG that does not recover with prolonged dark adaptation. Larger patchlike flecks and less severe impairment of night vision characterize the rarely reported fleck retina of Kandori. The differential diagnosis of flecked retina syndromes can be difficult using routine ophthalmologic examinations. In some cases of FA with progressive cone dystrophy, the signs and symptoms may be non-specific, which can lead to misdiagnosis. Electrophysiological findings and appropriate genetic analysis are essential tools in the differential diagnosis of FA.

Oguchi disease and FA are both types of congenital stationary night blindness, but each has a distinctively different fundus appearance. The fundus in Oguchi disease shows a peculiar yellowish iridescent sheen after light exposure that disappears after dark adaptation (i.e., Mizuo-Nakamura phenomenon). The pathogenesis of Oguchi disease appears to be a defect in rod neural adaptation; whereas, the pathogenesis of FA is thought to be a defect in regeneration of visual pigments. In addition, there is a group of diseases that are referred to as white dot syndromes that can be misdiagnosed as flecked retina syndromes. White dot syndromes are characterized by white lesions in the RPE and/or choroidal layers. The etiology of these disorders is not well established, but these syndromes are suspected to be inflammatory in origin and can be associated with uveitis[14].

The presence of myriad, discrete, round, whitish-yellow spots in the retina has been clinically described as being at the level of the RPE[6]. The spots in the posterior pole have a discrete appearance, and tend to decrease in number with age. In younger patients, spots are larger, they present in both the mid and far periphery, and they tend to be confluent. With increasing age, spots may be smaller, more discrete, and less apparent in the far periphery[3]. Disappearance of whitish-yellow spots in FA patients was reported to be associated with increasing age and/or post-uveitis[12,15]. Presentation of normal fundus has been reported in FA cases that were proven by typical ERG findings and genetic analysis that confirmed RDH5 mutation[3]. Retinal flecks are hypothesized to be the effect of an accumulation of toxic retinyl esters in the RPE that results from 11-cis-RDH disruption[15].

Fundus autofluorescence, spectral domain optical coherence tomography (SD-OCT), and scanning laser ophthalmoscope (SLO)

Autofluorescence imaging can demonstrate both hyperautofluorescent spots and low auto-fluorescence[3]. Hypofluorescence suggests that the spots do not represent lipofuscin[16,17]. Further studies that measure absolute levels of autofluorescence are needed. SD-OCT is an ideal tool for observing the position of retinol dots. Most dots extend from Bruch's membrane to the external limiting membrane. SD-OCT can also reveal abnormalities in the outer retina and disruption in the line representing the junction between the photoreceptor inner and outer segment (IS/OS) in some cases of FA. Long-term follow-up using SD-OCT should be studied in the future to reveal any longitudinal changes in the retinal structure of these spot lesions. The adaptive optics scanning laser ophthalmoscope (AO-SLO) revealed that macular cone density is reduced and the regularity of the macular cone mosaic spatial arrangement is disrupted in eyes with FA[16,17]. Given these results, AO-SLO may provide a method to detect early signs of macular phenotype in FA.

Electrophysiological findings

Scotopic ERG responses were reduced after a conventional 20 to 30 minutes period of dark adaptation, but typically become larger or normalized after prolonged dark adaptation (longer than two hours)[3,7,9]. Carr et al reported that the basic pathogenesis mechanism in FA was delayed regeneration of rod visual pigments[8]. Cone responses are usually normal if FA is not accompanied by macular dystrophy. However, many studies found and reported that some patients had reduced cone ERG and progressive cone dystrophy[3,7,18]. Niwa et al suggested that mutation in the RDH5 gene is involved in the regeneration of both rod and cone visual pigments[7,9]. The degree of cone dysfunction tended to be more severe in older patients, mainly due to the extensive loss of cone photoreceptors[7]. Further studies are warranted to identify the exact mechanism of cone-rod degeneration caused by RDH5 mutations.

Genetic analysis

FA is almost always caused by mutations in the RDH5 gene[7]. Since the first identification of mutation in the RDH5 gene was discovered by Yamamoto et al in 1999[9], there have been other reports of missense, inflame, and frameshift mutations[1,3,7,12,19,20]. The RDH5 gene is located on chromosome 12q13-q14[2,9] and it encodes the 11-cis-RDH enzyme, which is abundantly found in the smooth endoplasmic reticulum of RPE. This enzyme, which has 318 amino acids, is stereospecific for oxidizing 11-cis retinol to 11-cis retinaldehyde, the universal vertebrate chromophore of visual pigments[21]. The 11-cis-RDH is, therefore, the key enzyme in the visual cycle. The activities and stability of this enzyme are markedly decreased after RHD5 mutation. A reduction of 11-cis reinaldehyde in RPE and photoreceptors is indicated by a lack of retinol autoflorescence[4]. The residual function of RDH5 and other RDHs likely occurs in the late recovery of the visual cycle[2,4]. To date, at least 100 patients with FA and 44 mutations in the RDH5 gene have been reported worldwide from different ethnic groups[2]. Among the 44 reported mutations, the most frequent mutation was p.Leu310GluVal, with an allele frequency of 75%, and all patients carried at least one frequent allele[2]. This p.Leu310GluVal mutation, however, has only been reported in Japanese patients[19,20,22]. More than half of the 44 reported RDH5 gene mutations were found among Japanese families[3]. Reported cases of FA from many countries may expand our knowledge of FA among different races and ethnicities. To date, no significant association has been identified between the type of RDH5 mutation and severity of disease phenotype[3,7]. Long-term follow-up evaluation of fundus appearance will yield further evidence and understanding regarding the phenotype and progression of RDH5 retinopathy. In addition, retinaldehyde-binding protein 1 (RLBP1)[23] and RPE-specific protein (RPE65)[24] are also reported to demonstrate causal mutations associated with FA.

Treatment

A few studies in the treatment of FA have been reported. As a treatment strategy to restore physiologic levels of retinoids, administration of 9-cis-retinol may have a beneficial effect in those with RDH5 retinopathy. An FA mouse model that was used to study treatment with 9-cis-retinol showed improvement in visual function[25]. Another study that treated FA patients with high-dose 8-cis-β-carotene for 90 days also showed improvement in visual function[26]. That study, however, was performed in only seven cases, with a non-randomized design and no placebo control group. The ability of retinal function to fully recover after extended dark adaptation suggests that FA may be a suitable candidate for gene replacement therapy. To date, an effective treatment has not yet been established. Further investigations are required to identify a successful treatment in these patients.

Conclusion

The patient profiled in this case report has had stationary night vision impairment since childhood. Fundoscopy revealed numerous small subretinal whitish-yellow spots throughout the retina, but not in the macular area. Standard full-field ERG revealed significant reduction in rod responses that then recovered to normal or near-normal after prolonged dark adaptation (longer than two hours). Unfortunately, our patient declined our request for her to donate DNA for genetic analysis. As such and regrettably, genetic study of RDH5 mutation could not be conducted in this case. However, characteristic fundus abnormalities and the distinctive ERG findings of delayed regeneration of rod visual pigments strongly substantiate a diagnosis of FA. This is a rare congenital form of night blindness. Based on our review of the literature, this is the first reported case of FA in Thailand. The collection and analysis of genetic mutation data from future cases of FA in Thailand will improve our knowledge about mutations in this disorder among different ethnicities and races. Knowledge relating to the natural history,

variability, progression, electrophysiologic features, and genetic analysis of this disorder will assist in the identification of additional cases, facilitate accurate counseling, and will help to improve diagnostic methods and therapeutic interventions.

What is already known on this topic?

FA is a rare autosomal recession form of congenital stationary night blindness that has characteristic fundus and electrophysiologic findings. Most cases of FA are caused by mutations in the RDH5 gene, which encodes 11-cis retinal dehydrogenase, an essential enzyme for regeneration of visual pigments in the retina.

What this study adds?

Based on our review of the literature, this is the first reported case of FA in Thailand. This will inspire ophthalmologist to recognize this rare disease in fleck retina fundus. The collection and analysis of genetic mutation data from future cases of FA in Thailand will gain the knowledge about mutations in this disorder among different ethnicities and races. This will facilitate therapeutic interventions such as gene therapy in the future.

Acknowledgment

The authors gratefully acknowledge Miss Mathuwan Srikong (from the Medical Education Technology Center of the Faculty of Medicine Siriraj Hospital, Mahidol University) for preparation of the pictures and electrophysiologic recordings included in the present report.

Potential conflicts of interest

None.

References

1. Nakamura M, Lin J, Miyake Y. Young monozygotic twin sisters with fundus albipunctatus and cone dystrophy. Arch Ophthalmol 2004; 122: 1203-7.
2. Liu X, Liu L, Li H, Xu F, Jiang R, Sui R. RDH5 retinopathy (fundus albipunctatus) with preserved rod function. Retina 2015; 35: 582-9.
3. Sergouniotis PI, Sohn EH, Li Z, McBain VA, Wright GA, Moore AT, et al. Phenotypic variability in RDH5 retinopathy (fundus albipunctatus). Ophthalmology 2011; 118: 1661-70.
4. Schatz P, Preising M, Lorenz B, Sander B, Larsen M, Eckstein C, et al. Lack of autofluorescence in fundus albipunctatus associated with mutations in RDH5. Retina 2010; 30: 1704-13.
5. Carr RE. Congenital stationary nightblindness. Trans Am Ophthalmol Soc 1974; 72: 448-87.
6. Dryja TP. Molecular genetics of Oguchi disease, fundus albipunctatus, and other forms of stationary night blindness: LVII Edward Jackson Memorial Lecture. Am J Ophthalmol 2000; 130: 547-63.
7. Niwa Y, Kondo M, Ueno S, Nakamura M, Terasaki H, Miyake Y. Cone and rod dysfunction in fundus albipunctatus with RDH5 mutation: an electrophysiological study. Invest Ophthalmol Vis Sci 2005; 46: 1480-5.
8. Carr RE, Margolis S, Siegel IM. Fluorescein angiography and vitamin A and oxalate levels in fundus albipunctatus. Am J Ophthalmol 1976; 82: 549-58.
9. Yamamoto H, Simon A, Eriksson U, Harris E, Berson EL, Dryja TP. Mutations in the gene encoding 11-cis retinol dehydrogenase cause delayed dark adaptation and fundus albipunctatus. Nat Genet 1999; 22: 188-91.
10. Gonzalez-Fernandez F, Kurz D, Bao Y, Newman S, Conway BP, Young JE, et al. 11-cis retinol dehydrogenase mutations as a major cause of the congenital night-blindness disorder known as fundus albipunctatus. Mol Vis 1999; 5: 41.
11. Marmor MF. Long-term follow-up of the physiologic abnormalities and fundus changes in fundus albipunctatus. Ophthalmology 1990; 97: 380-4.
12. Yamamoto H, Yakushijin K, Kusuhara S, Escano MF, Nagai A, Negi A. A novel RDH5 gene mutation in a patient with fundus albipunctatus presenting with macular atrophy and fading white dots. Am J Ophthalmol 2003; 136: 572-4.
13. Walia S, Fishman GA, Kapur R. Flecked-retina syndromes. Ophthalmic Genet 2009; 30: 69-75.
14. Skorczyk-Werner A, Pawlowski P, Michalczuk M, Warowicka A, Wawrocka A, Wicher K, et al. Fundus albipunctatus: review of the literature and report of a novel RDH5 gene mutation affecting the invariant tyrosine (p.Tyr175Phe). J Appl Genet 2015; 56: 317-27.
15. Imaizumi M, Tatewaki SY, Kimoto K, Takaki Y, Nakatsuka K, Furushima M, et al. Disappearance of puncta after uveitis in an eye with fundus albipunctatus. Retina 2005; 25: 1096-8.
16. Makiyama Y, Ooto S, Hangai M, Ogino K, Gotoh N, Oishi A, et al. Cone abnormalities in fundus albipunctatus associated with RDH5 mutations assessed using adaptive optics scanning laser

ophthalmoscopy. Am J Ophthalmol 2014; 157: 558-70.
17. Song H, Latchney L, Williams D, Chung M. Fluorescence adaptive optics scanning laser ophthalmoscope for detection of reduced cones and hypoautofluorescent spots in fundus albipunctatus. JAMA Ophthalmol 2014; 132: 1099-104.
18. Miyake Y, Shiroyama N, Sugita S, Horiguchi M, Yagasaki K. Fundus albipunctatus associated with cone dystrophy. Br J Ophthalmol 1992; 76: 375-9.
19. Sekiya K, Nakazawa M, Ohguro H, Usui T, Tanimoto N, Abe H. Long-term fundus changes due to Fundus albipunctatus associated with mutations in the RDH5 gene. Arch Ophthalmol 2003; 121: 1057-9.
20. Wang C, Nakanishi N, Ohishi K, Hikoya A, Koide K, Sato M, et al. Novel RDH5 mutation in family with mother having fundus albipunctatus and three children with retinitis pigmentosa. Ophthalmic Genet 2008; 29: 29-32.
21. Parker RO, Crouch RK. Retinol dehydrogenases (RDHs) in the visual cycle. Exp Eye Res 2010; 91: 788-92.
22. Wada Y, Abe T, Fuse N, Tamai M. A frequent 1085delC/insGAAG mutation in the RDH5 gene in Japanese patients with fundus albipunctatus. Invest Ophthalmol Vis Sci 2000; 41: 1894-7.
23. Naz S, Ali S, Riazuddin SA, Farooq T, Butt NH, Zafar AU, et al. Mutations in RLBP1 associated with fundus albipunctatus in consanguineous Pakistani families. Br J Ophthalmol 2011; 95: 1019-24.
24. Schatz P, Preising M, Lorenz B, Sander B, Larsen M, Rosenberg T. Fundus albipunctatus associated with compound heterozygous mutations in RPE65. Ophthalmology 2011; 118: 888-94.
25. Maeda A, Maeda T, Palczewski K. Improvement in rod and cone function in mouse model of Fundus albipunctatus after pharmacologic treatment with 9-cis-retinal. Invest Ophthalmol Vis Sci 2006; 47: 4540-6.
26. Rotenstreich Y, Harats D, Shaish A, Pras E, Belkin M. Treatment of a retinal dystrophy, fundus albipunctatus, with oral 9-cis-β-carotene. Br J Ophthalmol 2010; 94: 616-21.

Fundus albipunctatus: รายงานผู้ป่วย 1 ราย ในประเทศไทย และทบทวนบทความ

งามแข เรืองวรเวทย์, อติพร ตวงทอง, ณัชชา จันทร์วราภา

Fundus albipunctatus จัดเป็นโรคหนึ่งของกลุ่มโรคที่ผิดปกติของการมองเห็นในที่มืดที่มีอาการคงที่และเป็นแต่กำเนิด โดยมีลักษณะเฉพาะของจอตาและการตรวจพบของคลื่นไฟฟ้าที่จอตา จอตาจะมีลักษณะเห็นเป็นจุดขาว-เหลือง จำนวนมากกระจายตัวอยู่ในชั้น retinal pigment epithelium โดยรอบของจอตา การตรวจคลื่นไฟฟ้าของจอตาจะพบลักษณะเฉพาะของโรคนี้ คือ การทำงานของ rod cell จะลดลงในที่มืดและจะกลับมาเป็นปกติ ถ้าให้ผู้ป่วยอยู่ในที่มืดนานมากกว่า 2 ชั่วโมง โรคนี้เกิดจากความผิดปกติของ RDH5 gene ซึ่งมีความสำคัญต่อการมองเห็น ปัจจุบันมีรายงานผู้ป่วยเพียงประมาณ 100 ราย และพบความผิดปกติของสารพันธุกรรม 44 รูปแบบทั่วโลก โรคนี้พบได้น้อยมากและมีการถ่ายทอดทางพันธุกรรมแบบ autosomal recessive ผู้นิพนธ์รายงานผู้ป่วย 1 ราย ในประเทศไทยพร้อมทบทวนบทความ