• Basic Research •

Atypical Adams-Oliver syndrome with typical ocular signs of familial exudative vitreoretinopathy

En-Zhong Jin, Lyu-Zhen Huang, Ming-Wei Zhao, Hong Yin

Department of Ophthalmology, Ophthalmology & Optometry Center, Peking University People's Hospital, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroidal Diseases, Beijing 100044, China

Correspondence to: Hong Yin. Department of Ophthalmology, Ophthalmology & Optometry Center, Peking University People's Hospital, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroidal Disease, Xizhimen South Street 11, Xi Cheng District, Beijing 100044, China. yinhong6386@163.com

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Abstract

● **AIM:** To report an atypical Adams-Oliver syndrome (AOS) family with typical ocular signs of familial exudative vitreoretinopathy (FEVR).

● **METHODS:** A patient with visible avascular area and obvious non-perfusion zone in the peripheral retina with systemic signs of AOS was reported. Familial and personal characteristics were collected for the patient and his sister. Gene sequencing and ophthalmic examinations including fluorescein angiography were all performed for the whole family.

● **RESULTS:** Two novel mutations of *DOCK6* (c.1396C>T and c.4796G>A) were identified in the proband and his family, and two compound heterozygous mutations were revealed in the proband and his sister. The patient and his sister showed physical deformities and mental abnormalities while FEVR mimicking retinal disorder can also be defined. No remarkable ocular or systemic abnormality can be observed for their parents. Peripheral retinal non-perfusion area, obvious abnormal vascularization or even retinal fold were observed in the proband and his sister, while only small avascular zone was identified for their parents.

● **CONCLUSION:** This is the first genetic authenticated AOS case mimicked as FEVR with genetic sequencing of a family. For the patients with ocular phenotype of FEVR, further examination should be performed if the systemic or mental abnormalities exist.

● **KEYWORDS:** Adams-Oliver syndrome; familial exudative vitreoretinopathy; gene sequencing; *DOCK6*; mutation

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INTRODUCTION

Adams-Oliver syndrome (AOS) is a rare inherited condition first described in 1945[1]. As a multiple malformation syndrome, AOS was characterized by a combination of aplasia cutis congenita (ACC) and variable degree of transverse limb defects[1]. Several genes associated with AOS including *DOCK, ARHGAP31, EOGT, RBPJ,* and *NOTCH* have been reported in the past decade[2-10]. In previous studies, the systemic phenotype within families of AOS may range from no obvious clinical manifestations in mutation carriers to severe multiple-system anomalies that can even result in miscarriage or stillbirth[1].

The AOS associated with ocular findings is rarely reported especially for the patients initially diagnosed in Ophthalmology Department. Almost all reports associated with ocular disorders were cases. In a previous literature, a female AOS case with bilateral congenital cataract was reported[3]. In another report, a case of AOS mimicked as familial exudative vitreoretinopathy (FEVR) had been reported recently, but genetic testing was not performed in this single case[11]. In 2012, an AOS case presenting retinal findings consistent with ischemic-proliferative retinopathy had also been reported[12]. Since AOS was found to be associated with several ocular disorders and few cases have already been reported, the relationship between AOS and ocular diseases worth further discussion.

In our present report, a family of AOS with ocular signs of FEVR was identified according to the clinical and genetic findings with *DOCK6* mutation. The ophthalmic examinations and gene sequencing were performed for the patient, his elder sister and their parents.

MATERIALS AND METHODS

Ethical Approval This study was approved by the Ethical Review Committee of Peking University People's Hospital (Beijing, China), which was conducted in accordance with the Declaration of Helsinki. Written informed consent for genetic

testing and medical photograph collection was obtained from the parents.

Patients A 5-year-old boy initially diagnosed with FEVR and found to have AOS according to the systemic situation, family history and gene sequencing was described. The individual and family investigation were performed. All family members of the proband boy including the parents and his 10-year-old sister were included in the present study and underwent ocular and genetic examinations for further analysis.

Ophthalmic Examinations Ophthalmologic examination was performed with a standard protocol including best-corrected visual acuity (BCVA), slit-lamp examination, binocular indirect ophthalmoscope fundus examination, ultra-wide-field fundus photography and fluorescein angiography (FA; Optos Daytona, Optos PLC, Dunfermline, UK). All the examination data was collected along with the data of medical history. All the digital images of fundus and FA were blinded reviewed by two experienced ophthalmologists (Yin H and Jin EZ).

Sequencing Whole exome sequencing was performed to characterize mutations for the proband boy and all his family members. Peripheral blood samples were obtained for the gene sequencing and sent to an external service to be sequenced.

RESULTS

The 5-year-old boy was found to have abnormal eye position and slightly mental retardation from birth according to his parents' discription. No physical deformitie and mental abnormalities existed among his parents. For further family members' investigation, his 10-year-old sister previously defined as retinal detachment and clinically diagnosed with FEVR. She was found to have poor vision, esotropia, blepharophimosis, upward of external eye corner, mild mental retardation and left hemiplegia.

The boy born at full-term with birth weight of 3000 g, and no special prenatal history was recorded. The rough visual acuity of the boy was 20/80 for both eyes with poor cooperation. Non-contact intraocular pressure was 17 mm Hg and 16 mm Hg for right and left eye, respectively. The cycloplegic refraction was measured as follows: -0.25 D for the right eye and -4.00 D for the left eye. No obvious abnormalities can be observed for the examination of the anterior segment of the eyes. For the binocular indirect ophthalmoscope fundus examination, normal boundary and color of the optic discs can be showed, while the avascular area was visible in the periphery retina. Ultra-wide-field FA examination was performed for the patient and obvious non-perfusion in the peripheral retina can be defined. Abnormal vessels can be observed at the junction of vascular and avascular retina though no leakage was identified (Figure 1).

Fundus color photographs and FA images were also collected for the boy's elder sister and parents. For the sister, significant peripheral retinal detachment can be observed in both eyes with temporal retinal folds originating from the optic disc, and the temporal retina was gray-white with hyperpigmentation sounded. FA examination showed peripheral retinal non-perfusion area and abnormal vascularization including tortuous veins, arteriovenous shunt, abnormal anastomosis. Retinal atrophy and hyperpigmentation can also be identified in fluorescein angiogram (Figure 2).

For their parents, the FA examinations were also performed. Only avascular zone and abnormal anastomosis at the vascular-avascular junction can be identified for them and both of them can reached a BCVA of 20/20. Meanwhile, no physical deformitie and mental abnormalities existed among the parents.

The genetic sequencing was performed for the whole family and the results indicated that the children (both the boy and his sister) had two compound heterozygous mutations (c.1396C>T p.R466X, c.4796G>A p.W1599X) in the gene *DOCK6* associated with AOS type 2, and the family verification results showed the two heterozygous mutations were originated from their father and mother, respectively. Pedigrees of the family and sanger confirmation of the identified *DOCK6* variants in proband with family members are shown in Figure 3.

DISCUSSION

AOS was not frequently reported in patients with ocular disorders though some isolated cases had been described associated with congenital cataract and retinal findings[12-18]. In our case, we described a family of AOS with all the members showing retinal signs similar to FEVR and *DOCK6* mutations. To the best of our knowledge, this is the first report of AOS family identified by gene mutations with mimicking FEVR retinal findings.

For the previous reports, the retinal fold with or without retinal detachment had been reported in AOS patients, and the retinal folds involving the macular was also described in one case[12,19]. A seven-week-old full-term infant within normal birth weight clinically diagnosed with AOS with ocular signs similar to FEVR was reported[11]. While no remarkable change existed in anterior segment, a radial falciform retinal fold extending from the macula to temporal periphery can be defined in this case. Significant preretinal fibrous proliferation can be noted, but no neovascularization or exudation were observed, and no ophthalmic examination was performed for the parents and three male siblings of the infant[11]. In our case, the whole family underwent gene sequencing and ophthalmic examinations, and genetic mutations can be identified accurately. Retinal detachment accompanied by retinal fold can also be found in the sister, along with poor vision, mild mental retardation and left hemiplegia. The ocular and systemic disorders of the sister confirmed by the genetic sequencing can further assist the diagnosis of AOS for the whole family.

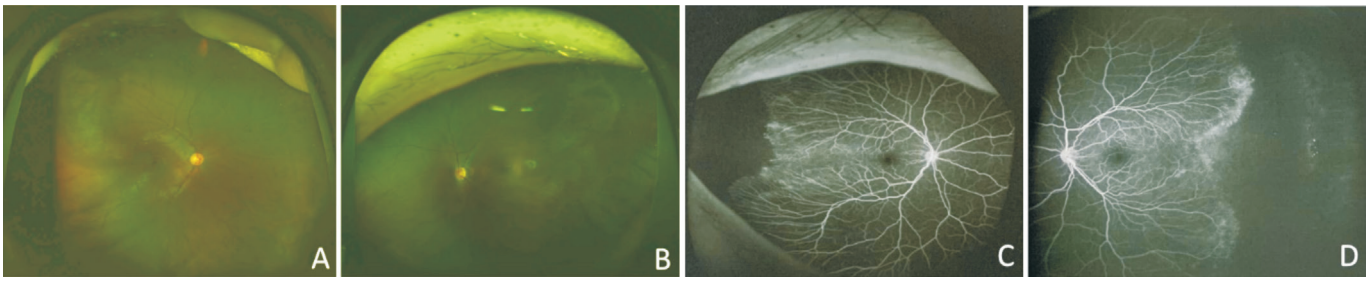

Figure 1 Fundus photograph and fluorescein angiogram of the patient A, B: Fundus photograph of the patient showing avascular zone of the temporal retina; C, D: Fluorescein angiogram of the patient showing peripheral retinal nonperfusion.

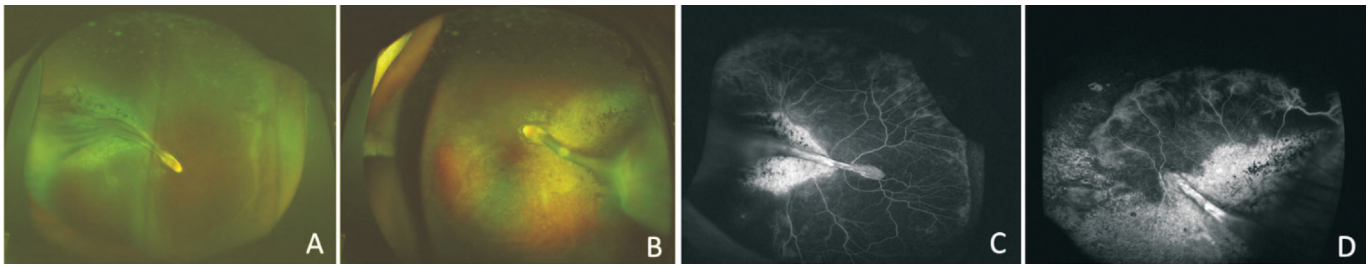

Figure 2 Fundus photograph and fluorescein angiogram of the patient's sister A, B: Fundus photograph of the patient's sister showing retinal fold involving macular, retinal atrophy, temporal retinal detachment and obvious pigmentation around; C, D: Fluorescein angiogram of the patient's sister depicting focal abnormal hyperfluorescence and peripheral nonperfusion.

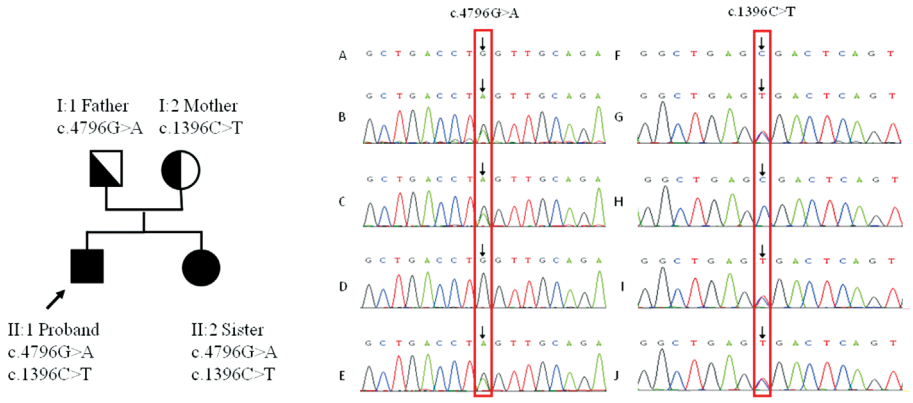

Figure 3 Pedigrees of the family with mutations in this study and the chromatograms of c.4796G>A and c.1396C>T in the proband and his family A-E: Chromatograms of c.4796G>A; F-J: Chromatograms of c.1396C>T. A, F: Reference sequences; E, J: Sequences of the proband; B, G: Sequences of the proband's sister; C, H: Sequences of the proband's father; D, I: Sequences of the proband's mother. B, C and E showing c.4796G>A existed in the whole family except the mother; G, I and J showing c.1396C>T existed in the whole family except the father.

In this case, FEVR-like fundus and fluorescein angiogram can be observed in all family members. Despite the presence of FEVR-like changes existed, they were generally quiet. No obvious peripheral leakage or retinal traction can be observed, and the boy was only asked for closely and regular follow-up without treatment.

In this case, the parents of the boy showed no obvious ocular symptoms or signs, but the boy showed slightly lower intelligence, poor vision, mild esotropia and large non-perfusion zone at the temporal retina, which suggesting FEVR-like fundus changes. For the family history, it was found that the child's sister had a history of retinal detachment with retinal fold in both eyes. Fundus examinations showed obvious retinal folds in both eyes, with small palpebral fissure, esotropia, raised outer corner of the eye, right hand penetrating palm, high muscle tension, mild hemiplegia of the left limb, *etc*. There are many similarities between these manifestations and the previously reported systemic and ocular signs of AOS[1].

Basing on the ocular and systemic manifestations of the boy and his sister, a whole-exome sequencing analysis of the single-gene disease was performed on the whole family. On one hand, further clarification whether there are FEVR-related genetic changes were performed, and on the other hand, it is also analyzed whether there was genetic mutation associated with AOS. The sequencing revealed that the proband had two heterozygous mutations (c.1396C>T p.R466X, c.4796G>A p.W1599X) in *DOCK6* which is associated with the AOS type

2. Though the variant in *DOCK6* was reported to be associated with AOS type 2 before, these two novel missense mutations identified in this study had not been previously registered in the Ensembl database (http://www.ensembl.org/index.html) or the Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php)[10]. And the compound heterozygous mutations of them were found to be associated with the AOS proband. The further family verification results showed that the two heterozygous mutations came from their parents respectively and were compound heterozygous mutations. The sister also carries the two compound heterozygous mutations. As truncating mutations, the two novel missense mutations show high potential pathogenicity. Our findings expand the mutational spectrum of *DOCK6* and suggest that the two compound heterozygous mutations of *DOCK6* is associated with AOS.

As we all know, AOS was first reported in 1945, mainly manifested as scalp defects and varying degrees of limb defects[1]. The AOS syndrome can be inherited in autosomal dominant manner in most cases, and in autosomal recessive manner for some cases (*EOGT* and *DOCK6* gene mutations)[2-5]. The underlying pathological mechanism of AOS is considered as a congenital vascular disease that may involve multiple systems such as the cardiovascular system, brain, liver, lung, eyes and skin[6]. In the past, few reports about AOS related to ocular disorders, especially for retinal manifestations[11]. The insufficient evidence between AOS and retinal disorders like FEVR made the present study more meaningful. But the limitations of our study can not be ignored. First, only one family of AOS mimicked FEVR was included which may reduce the persuasion, more families or cases should be collected and combined analyzed. Second, as a report of family case, no functional validation was performed even though two novel mutations were found. Third, the ocular signs of FEVR of the proband and his sister was typical while the AOS signs of them were atypical, but the genetic sequencing can provide most strong evidence.

As an inherited retinal disorder characterized by abnormal development of retinal vasculature, FEVR was thought to be associated with Wnt signaling pathway[20-21]. Several genes including *NDP, FZD4, LRP5*, and *TSPAN12* had been found to be associated with FEVR in previous studies[22-26]. On the other hand, these genes were also identified in atypical retinopathy of prematurity (ROP) patients[27-28]. The Wnt signaling pathway may play a common pathological role in them, which is a major role for the development of retinal vascular. According to the whole-exome sequencing analysis, no special mutations of these genes can be found in our present family case, which did not support the relationship between AOS and Wnt signaling pathway. Since no association between FEVR and *DOCK6* had been identified before, and the *RBPJ* and *NOTCH* involved in the Notch signaling pathway were found to play a crucial role in developing blood vessel walls, the pathogenesis of AOS may be different with FEVR[19,29-30]. Although a case of AOS with similar changes mimicking FEVR diagnosed basing on clinical systemic characteristics has been reported, the present case is the first confirmed family case basing on genetic sequencing. Our report provides information on genetic mutations and clinical features to assist the ophthalmologists in recognizing AOS patients. Also, this family case can help us further understanding the ocular manifestations of AOS. It can be defined that the ocular phenotype of AOS may mimic that of FEVR. The patients diagnosed with AOS should be further evaluated for the retinal vasculopathy by fundus examinations including fluorescein angiography to make sure whether specific treatment was required. And the FEVR patients should also be carefully evaluated for the potential possibility of suffering from AOS.

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