Unique phenotypic–genotypic correlation in Saudi patients with *ALMS1* mutations

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Abstract:

Mutations in the *ALMS1* gene have been linked to isolated inherited retinal dystrophy or Alström syndrome. This report illustrates the unique pattern of *ALMS1*-associated diseases in a set of three simplex Saudi patients originating from unrelated consanguineous families. A detailed ophthalmological assessment was performed at the Department of Ophthalmology at King Saud University, Riyadh, Saudi Arabia. Next-generation sequencing vision panel revealed recessive *ALMS1* mutations (reference sequence NM_015120). As a result, three distinct pathogenic *ALMS1* mutations were identified; the first one is a nonsense mutation (c.8158C>T: p.R2720X) which has recently been identified in a Chinese patient, while the other two are known to have a founder effect in the Saudi population (the frameshift: C.848dupA: p.E283fs and the splicing: C.11870-2A>T: p.?). Clinically, a prominent nerve fiber layer was observed in the three studied patients with variable expectations of vessel attenuation. In addition, two of our patients observed unusual presentation of specific retinal pigment epithelium pigmentations in semi/halo-arrangement around the macula. Thus far, our report expands the phenotypic–genotypic spectrum of *ALMS1*-associated diseases and supports the principles of applying precision medicine in Saudi Arabia by utilizing the fact that common founder mutations were identified and unique phenotype was observed.

Keywords:

ALMS1 gene, Alstrom syndrome, cone-rod dystrophy, founder mutation, Leber congenital amaurosis

Introduction

Homozygous or compound heterozygous mutations in the *ALMS1* gene have been always linked to Alström syndrome (OMIM: 203800).[1] Patients with Alström syndrome are characterized by a wide spectrum of systemic disorders including severe early-onset inherited retinal dystrophy (IRD) of either Leber congenital amaurosis (LCA) or cone-rod dystrophy (CRD), childhood obesity, hyperinsulinemia with type 2 diabetes mellitus, cardiac and hepatic dysfunction, sensory neural hearing loss, and renal failure. In contrast, recent studies showed that *ALMS1* could be regarded also as a candidate causative gene in patients diagnosed with an isolated form of IRD.[2]

In this report, three simplex cases from three unrelated consanguineous families of first-degree cousins were referred to the Department of Ophthalmology at King Saud University in Riyadh, Saudi Arabia. The affected patients were noted to have poor vision, photophobia, and nystagmus with or without systemic involvement since early childhood. A full ophthalmological examination was conducted on the three affected patients. Imaging for the evaluation of IRD includes color fundus photos, optical coherence tomography (OCT), and fundus autofluorescence. Full-field electroretinography (ERG) was particularly important in differentiating forms of IRD. Next-generation sequencing (NGS) vision panel revealed recessive *ALMS1* mutations (reference sequence NM_015120).

Case Reports

Case 1

A 13-year-old male presented with poor vision and photophobia noticed since birth. At 3 months of age, the parents noticed nystagmus. On examination, visual acuity was 20/400 in both

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eyes. Anterior segments including the cornea and lens were normal. Fundus examination showed a mild waxy pallor appearance of the optic disc with sectoral temporal optic atrophy, attenuated retinal vessels, and hyperpigmented macula with a minimal dispersed accumulation of flecks in a semi-crescent shape around the macula [Figure 1a and b]. OCT revealed retinal thinning with minimal inner and outer retinal layer atrophy, less pronounced at the fovea [Figure 1c and d]. The finding of an extinguished full-field ERG is confirmatory of the presence of LCA in our patient. The detailed systemic assessment revealed no obvious systemic signs of Alström syndrome. NGS vision panel screening has identified homozygous loss of function frameshift *ALMS1* variant (NM_015120: Exon5:c.848dupA: p.E283fs). This variant is known as a founder mutation in the Saudi population according to the unpublished data from Saudi human genome project and is considered to be pathogenic according to the American College of Medical Genetics (ACMG) guidelines.

Case 2

An 18-year-old male presented with poor central vision later followed by progressive loss in peripheral vision, photophobia, and hearing impairment since birth. Ophthalmological examination revealed visual acuity of light perception with poor light projection in four quadrants of both eyes. The cornea and lens were normal. Fundus examination showed pallor appearance of the optic disc, attenuated retinal vessels with generalized mottling of the retinal pigment epithelium (RPE) and peripheral intraretinal pigment migration, and pigmentary changes of the macula, and mid-peripheral pigmentation with prominent nerve fiber layers [Figure 2a and b]. During the course of the disease, full-field ERG showed abnormalities of both cone and rod responses, with cone responses typically more severely and more precociously affected than rod responses compatible with CRD. The audiological assessment revealed mild bilateral sensorineural hearing loss up to 1 kHz rising to normal hearing at higher frequencies. Cardiac assessments using echocardiography were normal. No other signs of diabetes or hepatic dysfunction part of Alström syndrome were noted. NGS vision panel screening has identified a novel homozygous splicing variant in *ALMS1* (NM_015120: Exon19: c.11870-2A>T: p.?). This variant is also known as a founder mutation in the Saudi population according to the unpublished data from Saudi human genome project and is considered to be pathogenic according to the ACMG guidelines.

Case 3

A 13-year-old male presented with poor vision and photophobia since birth. Ophthalmological examination revealed counting finger vision close to the face in both eyes and normal anterior segment. Fundus examination showed pallor of the optic disc with anomalous optic disc vessels more prominent in the left eye, with mild attenuated retinal vessels, and intraretinal/subretinal fleck deposits accumulated in a halo around the fovea with predominant central macular defect bilaterally [Figure 3a and b]. Full-field ERG showed abnormalities of both cone and rod responses, with cone responses affected more than rod responses compatible with CRD. Endocrinology assessments were found to have elevated C peptides while no sign of hyperglycemia was detected based on the negative glucose challenge test. Gastroenterological assessments showed elevated liver function tests. Other Alström syndrome manifestations such as heart failure and sensory neural hearing loss were negative. NGS vision panel screening confirmed that this patient harbored loss of function nonsense homozygous *ALMS1* variant (NM_015120: Exon10:c.8158C>T: p.R2720X). This variant was found to segregate with the disease phenotype and was considered to be pathogenic according to the ACMG guidelines. Moreover, this variant has recently been identified

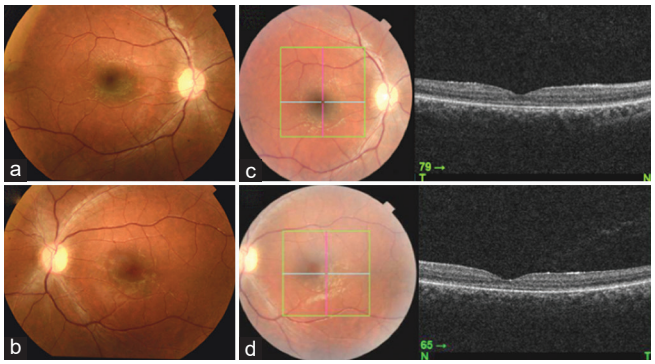

Figure 1: Case 1 (a and b): Color fundoscopic picture of right and left eye show mild optic disc pallor with prominent never fiber layer and semi-halo-shaped RPE flecks around the macula, (c and d) OCT of the right and left eye show thing of the mild thinning of the retinal layers. RPE: Retinal pigment epithelium, OCT: Optical coherence tomography

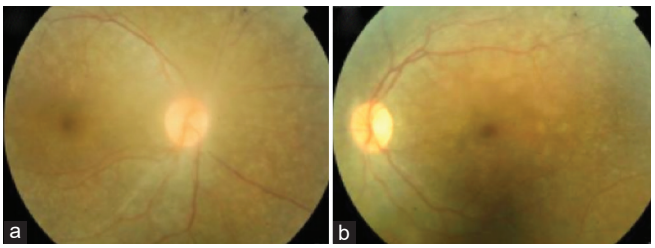

Figure 2: Case 2 (a and b): Color fundoscopic picture of right and left eye show generalized RPE mottling with prominent never fiber layer

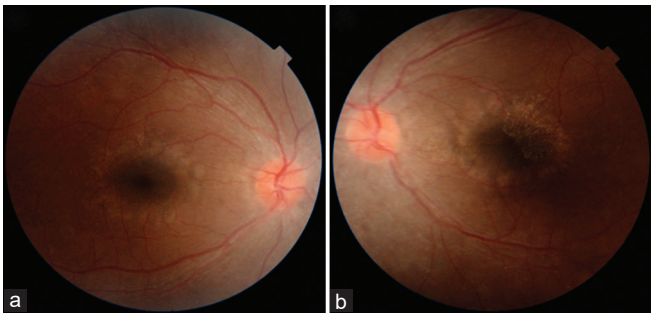

Figure 3: Case 3 (a and b): Color fundoscopic picture of right and left eye show anomalous optic disc vessels, prominent never fiber layer, and halo-shaped RPE flecks around the macula with clear macular defect bilaterally. RPE: Retinal pigment epithelium

in a Chinese patient who showed the full clinical spectrum of Alström syndrome.[3]

Discussion

In this report, we have characterized the variability of ocular and extraocular phenotypes of young patients who were molecularly confirmed to harbor recessive homozygous *ALMS1* mutations.

Our case report supports the phenotypic spectrum of Alstrom syndrome in which CRD was accompanied by the ciliary effect of the *ALMS1* gene that led to the childhood onset of bilateral sensorineural hearing loss in Case 2 and hepatic dysfunction in Case 3.[4,5] On the other hand, an isolated case of LCA was observed in Case 1 which is in line with the recent studies that linked *ALMS1* as a candidate causative gene in isolated LCA/CRD.[1,6,7] Although no other systemic dysfunction of Type 2 DM, cardiac and pulmonary dysfunctions were observed yet, a close follow-up is highly recommended for early detection of these life-threatening complications.

Interestingly, a unique ocular phenotype was observed clinically and further illustrated in color fundoscopic pictures of our studied Saudi subjects represented by; the presence of a prominent nerve fiber layer in our three patients; the presentation of mild attenuation of blood vessels in Cases 2 and 3 in contrast to the prominent vessels attenuation noted with *ALMS1* associated retinal dystrophy as in Case 1; the presence of the prominent RPE flecks around the macula that are arranged in a specific pattern of semi and whole halo-shaped RPE pigmentation as in Cases 1 and 3. This unique ocular phenotype seen in our Saudi patients is reported here for the first time with *ALMS1*-associated diseases and might highlight further clinical characterization of *ALMS1*-related ocular features.

In conclusion**,** the uniqueness of our report is illustrated by the fact that two out of the three studied subjects were found to harbor unique Saudi founder mutations based on the database of the Saudi genome project. In addition, the nonsense mutation was identified in the third patient highlighting a further level of locus heterogeneity and expanding the overall genetic spectrum of *ALMS1*-associated diseases.

The presence of common founder effects of *ALMS1* in the Saudi population will open the field to apply the principles of precision and personalized medicine in the near future by establishing targeting clinical therapeutic trials of gene therapy to treat these common variants in our Saudi population.

Lesson

Ophthalmologists should recognize that a young child with a biallelic mutation in the *ALMS1 g*ene could potentially harbor an underlying diagnosis of Alstrom syndrome, even when typical extraocular features are not yet apparent and the initial presentation is compatible with isolated LCA or CRD phenotypes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed

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Conflicts of interest

There are no conflicts of interest.

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