Saudi Journal of Ophthalmology (2017) xxx, xxx–xxx

Original Article

Severe retinal degeneration at an early age in Usher syndrome type 1B associated with homozygous splice site mutations in MYO7A gene

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Abstract

Purpose: Usher syndrome is the most common cause of deafness associated with visual loss of a genetic origin. The purpose of this paper is to report very severe phenotypic features of type 1B Usher syndrome in a Saudi family affected by positive homozygous splice site mutation *in MYO7A* gene.
Methods: Affected siblings went through detailed history. Complete ophthalmic examination was done. Imaging with colour fundus photography, fundus autofluorescence (AF), and optical coherence tomography (OCT) scans was performed. Full field electroretinogram (ffERG) was recorded. Molecular genetic testing was done using next-generation sequencing.
Results: Visual acuity was more reduced (range 20/300–20/40) in older siblings (age>30 years), than in younger (age <30 years) siblings (range 20/70–20/25). OCT scans showed macular atrophy in all but one case that has cystoid macular edema (CME). AF demonstrated atrophy outside a small foveal area showing high signal. FfERG was flat in all cases. The homozygous splice site mutation c.470+1G>A in intron 5 of the *MYO7A* gene was detected in all affected siblings.
Conclusions: This mutation manifested with advanced retinal degeneration at a young age. This may have implications regarding future gene therapy in Usher syndrome cases with this genotype.

Keywords: Usher syndrome, Retinitis pigmentosa, Electroretinogram, Fundus autofluorescence, *MYO7A* mutation

https://doi.org/10.1016/j.sjopt.2017.10.004

Introduction

Usher syndrome is the most common cause underlying genetically associated deafness and blindness. The syndrome is named after Charles Usher (a British ophthalmologist) and has an estimated incidence of 3–4.4 per 100,000 people.[1] The disorder is transmitted through an autosomal recessive inheritance and is clinically and genetically heterogeneous. Affected persons have congenital sensorineural hearing loss and progressive pigmentary retinopathy.[2]

The cilium is a common cellular organelle in the inner ear hair cells and photoreceptors of the retina. In Usher syndrome, a dysfunction of the cilium results in combined hearing loss and visual dysfunction.[3] Three clinical subtypes of

Received 9 September 2017; received in revised form 8 October 2017; accepted 17 October 2017; available online xxxx.

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Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

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Please cite this article in press as: Abdelkader E., et al. Severe retinal degeneration at an early age in Usher syndrome type 1B associated with homozygous splice site mutations in MYO7A gene. *Saudi J Ophthalmol* (2017), https://doi.org/10.1016/j.sjopt.2017.10.004

Usher syndrome have been identified, with mutations in different sets of genes. Usher syndrome type 1 (USH1) is the most severe of the three USH subtypes with profound hearing loss since birth, vestibular areflexia, and retinitis pigmentosa appearing at a prepubescent age.[4] Usher syndrome type 2 (USH2) displays moderate to severe hearing loss, absence of vestibular function, and later onset of retinal degeneration. Usher syndrome type3 (USH3) shows progressive postlingual hearing loss, variable onset of RP, and variable vestibular response.[5]

All three subtypes of Usher syndrome share the classic ophthalmologic findings seen in retinitis pigmentosa and are described as a triad of attenuated retinal blood vessels, waxy pallor of the optic disc, and intraretinal pigmentation in a bone-spicule pattern. Retinal vascular attenuation was found in 94% of 384 eyes and optic disc pallor in 52% in one series.[6] The macula becomes affected in moderate or advanced disease, when photoreceptor degeneration advances and leads to retinal thinning and loss of visual acuity. Cataracts, especially posterior subcapsular, affect approximately 50% of patients with retinitis pigmentosa. The vitreous may contain a dust-like pigmented substance, compromised of pigment granules. Complete vitreous detachment is more common than in normal subjects.[6]

Usher syndrome involves at least 12 loci among the three different clinical subtypes. Genes identified for the more commonly inherited loci include *MYO7A* (encoding myosin VIIa), *USH2A* (encoding usherin), *CDH23* (encoding cadherin 23), *PCDH15* (encoding protocadherin 15), *USH1C* (encoding harmonin), *USH3A* (encoding clarin 1), and *USH1G* (encoding SANS). Transcripts from all these genes are found in many tissues/cell types other than the inner ear and retina, but all are uniquely critical for retinal and cochlear cell function.[7]

MYO7A encodes for a large (2215 aminoacid actin-based) motor protein expressed in the cochlear hair cells as well as retinal photoreceptors and in the retinal pigment epithelium (RPE).[8] Although not fully understood, myosin VIIa is important for maintaining the structure and function of retinal photoreceptors and retinal pigment epithelium (RPE). In photoreceptors, it is involved in transport of Rhodopsin from the rod inner segments to the outer segments.[9] In the RPE, it is vital for localization of melanosomes in the apical microvilli and normal mobility of phagosomes.[10]

In this article we present the phenotypic features of 6 siblings of a Saudi family affected by Usher syndrome type 1B with a homozygous splice site mutation in *MYO7A* (MIM #276903) (MIM #276900).

Patients & methods

This is a retrospective study of a large consanguineous Usher syndrome family that consists of 12 children comprising 2 affected daughters, 4 affected sons, 3 unaffected daughters and 3 unaffected sons. The parents are from the same tribe with no history of vision or hearing problems. Informed consent for genetic testing and inclusion in the study was obtained from affected family members. Consent for inclusion in the study was obtained from non-affected family members except for the father who was not available for consultation. Institutional Review Board (IRB)/Ethics Committee approval at King Khaled Eye Specialist Hospital was obtained. The research adhered to the tenets of the Declaration of Helsinki. Table 1 summarizes the demographic and clinical findings in the 6 affected siblings.

The age range of the children was 17–40 years. The age of the affected siblings ranged from 17 to 38 years. A detailed medical and family history was obtained from their mother. This included information regarding age of onset of hearing loss and age of perceived night blindness (Table 1).

All the family members except the father underwent complete ophthalmologic examination including best-corrected visual acuity (VA), intraocular pressure (IOP) measurement, slit lamp examination, and dilated fundus examination. Color fundus photos were obtained for all cases using Topcon fundus camera (Top TRC-50DX). Fundus autofluorescence (AF) imaging was done for all cases using wide field Optos system (Optos 200TX) with 488 nm wavelength.

Retinal structure was analyzed qualitatively with transfoveal horizontal spectral domain optical coherence tomography scans (OCT, Heidelberg Engineering, Inc., Heidelberg, Germany) and wide field imaging (Optos PLC, Dunfermline, UK). Visual field testing was not done because of the severity of deafness and associated speech difficulties that made communication for testing difficult.

Retinal function was evaluated in affected siblings with full-field electroretinography (ffERG, Nicolet Biomedical Instruments, Madison, Wisconsin, USA), in dark adapted and light adapted state according to ISCEV standards,[11] with a few modifications as follows. Full-field electroretinograms were recorded in a Nicolet analysis system (Nicolet Biomedical Instruments, Madison, Wisconsin, USA), after dark adaptation of subjects for 40 min, dilatation of the pupils with topical cyclopentolate 1% and metaoxedrine 2,5% and topical anaesthesia, with a Burian Allen bipolar contact lens and a ground electrode applied to the forehead. Responses were

Table 1. Demographics, clinical, and imaging findings in affected siblings from a family with the homozygous donor splice site mutation c.470+1G>A in intron 5 of the *MYO7A* gene.

Case	II:2	II:3	II:4	II:8	II:11	II:12
Age (age of examination)	38	36	34	27	22	17
Gender	Female	Female	Male	Male	Male	Male
Age of onset of hearing loss	6 months	6 months	5 months	4 months	4 months	4 months
Age of onset of visual symptoms	6 years	6 years	6 years	5 years	5 years	5 years
BCVA OD	20/300	20/40	20/300	20/60	20/70	20/40
BCVA OS	20/300	20/40	20/200	20/50	20/60	20/25
IOP OD	17	17	15	13	13	10
IOP OS	16	15	14	11	13	11
Foveal thickness OD*	142	153	210	171	110	393
Foveal thickness OS*	130	193	199	153	95	340
ffERG	Non-recordable	Non-recordable	Non-recordable	Non-recordable	Non-recordable	Non-recordable

* Central subfield thickness in micro-meters on horizontal transfoveal spectral domain optical coherence tomographyscans. FfERG = Full field electroretinography. OD = right eye OS = left eye. BCVA = best corrected visual acuity.

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