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Cochlear implantation in individuals with Usher type 1 syndrome

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Summary

Objective: To analyze the occurrence of the Usher type 1 (USH1) gene mutations in cochlear implant recipients with deaf-blind Usher syndrome, and to assess the potential effect of these genes and other factors on the therapeutic outcome.
Study design: Case series study of nine patients with the phenotypic diagnosis of USH1.
Methods and subjects: Mutation analysis of four USH1 genes (*MYO7A*, *USH1C*, *CDH23*, and *PCDH15*) by single strand conformational polymorphism (SSCP) and direct sequencing methods. Pre- and post-implantation audiologic tests including pure tone audiometry, speech perception measures, and qualitative assessment of auditory performance. Nine USH1 patients who received their cochlear implants at the University of Miami Ear Institute, Miami, FL, USA, and at the Department of Cochlear Implants, Great Ormond Street Hospital for Children, London, UK.
Results: DNA samples from five of the nine patients were available for mutation analysis. Three of the five patients were found to carry USH1 mutations including two with a truncated mutation in *CDH23* and one being a digenic inheritance with mutations in *CDH23* and *PCDH15*. We may have failed to detect mutations in the amplicons analyzed, as neither SSCP nor direct sequencing, even combined, detects all mutations present. Our failure to detect mutations in all five patients may also confirm the genetic heterogeneity of USH1 and additional USH1 loci remain to be mapped. Pre-implantation assessment indicated that all of the subjects were pre-linguistically profoundly deaf, had no consistent response to sound, had varying degrees of auditory-oral habilitation. Age at implantation ranged from 2 to 11 years. There was post-implantation improvement in sound detection and speech recognition measures in

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closed-set format in all patients. Children implanted at an age of 3 years or less showed good open-set speech perception with lip-reading. All patients are implant users. Those patients who do not show open-set perception still use the cochlear implant as an adjunct of lip-reading or total communication.

Conclusion: Testing for mutations in the USH1 genes allows early identification and intervention of children with USH1; timely intervention is important to maximize the development of useful auditory-oral communication skills prior to the onset of the visual impairment.

1. Introduction

Usher syndrome (USH) is the most common genetic cause for the dual handicap of deafness and blindness. This autosomal recessive syndrome is characterized by sensorineural hearing impairment associated with retinitis pigmentosa (RP). USH is found in 3—6% of children with congenital deafness, and it may account for as much as 50% of the deaf-blind population [1,2]. Three distinct forms of USH (USH1—USH3) have been characterized [2,3]. The severity and progression of the hearing impairment and the presence of vestibular dysfunction distinguish the three types. USH1 is the most severe, with profound congenital deafness, constant vestibular dysfunction and a relatively severe form of RP associated with the onset of blindness in late childhood. Children with USH2 present with moderate to severe sensorineural hearing loss and normal vestibular function. The visual impairment in USH2 begins in the second decade of life and some patients maintain useful vision into middle age. USH3 presents with progressive hearing loss and varying degrees of vestibular dysfunction [3]. Of all USH patients worldwide, it is estimate that 33—44% have USH1 and 56—67% have USH2, while only a minority of patients have USH3 [4,5]. In Finland, however, USH3 is the most common type (40%), explained by genetic and geographical isolation accompanied with a founder mutation [6].

Virtually all members of the deaf community view the visual impairment that accompanies USH as a devastating handicap. Children with USH1 begin to develop decreased night vision in late childhood, ultimately leading to blindness in young adulthood. The progressive deterioration of visual acuity hinders the ability to use sign language. Since educational decisions are often made before the appearance of blindness, early diagnosis of USH1 is of importance to guarantee that parents receive the most appropriate counseling at the time of identification of the hearing loss. Some authors have recommended giving added weight to the decision of cochlear implantation and oral communication particularly in USH1 due to the severity of the dual handicap [7,8].

Clinically, the diagnosis of RP (and therefore of USH) can be made before the appearance of the visual symptoms by electroretinography (ERG). However, in young children, ERG is likely to involve the use of a general anesthetic, it is not widely available, and may be fraught with technical difficulties. Without good reason such test would not be carried out and the diagnosis of USH may be delayed. Screening for vestibular dysfunction is one way of selecting young children for the ERG test, as it has been proposed [9,10].

DNA markers are emerging as a non-invasive tool for the diagnosis of many types of hereditary hearing loss. Identification of gene tests for USH would be a useful way of identifying those children who needed further investigations and assuring that they are diagnosed early enough to give them maximum rehabilitative care. To date, 11 chromosomal loci have been mapped for USH. In regards to USH1, seven loci (USH1 subtypes "A" through "G") have been mapped to the following chromosomal regions: 14q32, 11q13.5, 11p15.1, 10q, 21q21, 10q21-22, and 17q24-25 [11]. So far, the causative genes have been identified for USH1B, USH1C, USH1D, USH1F, and USH1G. They encode the following proteins, respectively: MyosinVIIA [12], a PDZ-containig protein (harmonin) [13,14], cadherin 23 [15], protocadherin 15 [16], and scaffold protein containing *an*kyrin repeats and SAM domain, SANS [17]. Mutations affecting these proteins cause deafness and vestibular dysfunction in humans by affecting the function of the inner ear mechanoreceptors for sound and motion signal transduction. There remain, however, some USH1 families that still fail to show linkage to any of these regions, underscoring the significant clinical and genetic heterogeneity of USH.

In the present study we perform mutational analysis in four USH1 genes (*MYO7A*, *USH1C*, *CDH23*, and *PCDH15*) in cochlear implant recipients with USH, and assess the potential effect of these genes and other factors on the therapeutic outcome. Since this