Genotype Phenotype Correlation in Usher Syndrome

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INTRODUCTION

Usher syndrome is a syndromic form of autosomal recessive hearing impairment that is characterised by sensorineural hearing loss, retinitis pigmentosa and variable vestibular function. Three clinical types and eleven genetic types have been identified making the condition clinically and genetically heterogeneous.

Type	Hearing loss	Peripheral Vestibular function	Onset of Retinitis pigmentosa
Type I	Profound	Absent	First decade
Type II	Moderate to severe	Normal	Second decade
Type III	Progressive	Variable	Variable

Table 1: Clinical classification of Usher syndrome[1]

AIM OF THE STUDY

The aim of this study was to perform a phenotypic genotypic correlation on a large group of subjects with Usher syndrome and correlate these findings to specific mutations in the Usher genes.

MATERIALS AND METHODS

Subject Recruitment: The National Collaborative Usher Study is a multicentre study that recruited 220 affected individuals from 182 families nationwide. All subjects underwent detailed audiovestibular and ophthalmological evaluation and provided blood samples for genetic analysis..

Audiological Evaluation

included pure tone audiometry, tympanometry, transient evoked otoacoustic emissions and auditory brainstem evoked responses. Severity of hearing loss was based on the average of pure tone thresholds at 0.25, 0.5,1,2 and 4kHz [2]. Tympanometry was used to assess normal middle ear function and the absence of retrocochlear involvement was confirmed by normal auditory brain stem evoked responses[3] (presence of ABR was dependent on the severity of hearing loss).

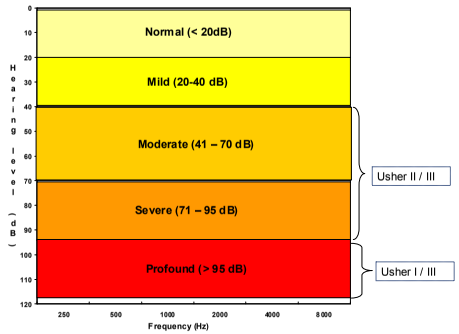


Fig 1: Severity of Hearing loss - mean HL (0.25, 0.5, 1, 2, 4 and 8kHz)

Vestibular Evaluation

Peripheral vestibular function was evaluated by videonystagmographic recording of eye movement responses to chair rotation and by caloric testing. Sinusoidal rotation was at 60°/sec and 0.05Hz and step velocity tested by accelerating to 60°/sec peak velocity within one second and decelerating at the same time [4]. Responses were considered normal if within two SD of departmental normative data. Canal paresis was calculated by Jongkees formula[5] (abnormal>20%)

Fig 2: Rotary chair & VNG recording to assess vestibular function

RESULTS

96 males and 106 females completed audiovestibular evaluation (N=202; Age range 3 to 68 years). Genetic results are currently available on 115 individuals. Overall classical phenotypic audiovestibular characteristics correlated well with identified genotype for clinical types I and II . Comparing individuals with and without identified known type I and II mutations showed no significant differences in hearing or balance function.

		Genetic diagnosis of Usher								
		Mutations to be confirmed	USH1B	USH1C	USH1D	USH1F	USH2A	USH2C	USH3	Total
Clin diagnosis of Usher type	1	25	12	2	4	3	0	0	0	46
	2	54	1	1	0	0	85	1	0	142
	3	8	0	1	0	0	2	0	3	14
Total		87	13	4	4	3	87	1	3	202

Table 2: Cross tabulation of clinical diagnosis* Genetic subtypes

Results of Pure tone audiometry

USHER TYPE I

The majority of those with confirmed mutations in USH1 genes had profound HL (N=19 + 2 CI). Three subjects had unexpectedly good hearing levels. Mr Pt1 had a heterozygous mutation in USH1B gene Mr Pt2 and sibling had compound heterozygous mutations in the USH1C gene

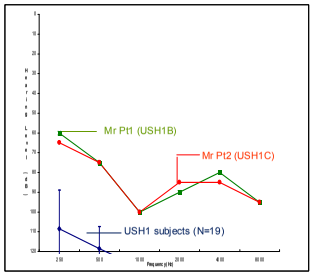


Fig 3: Pure tone hearing thresholds (air conduction) in subjects with USH1 mutations. Blue data points represent mean HL of 19 subjects. Hearing levels of Mr Pt1 in green and Mr Pt2 in red)

USHER TYPE II

87 Subjects had mutations in USH2A gene. The severity of hearing loss varied from moderate to severe with a wide range unrelated to age

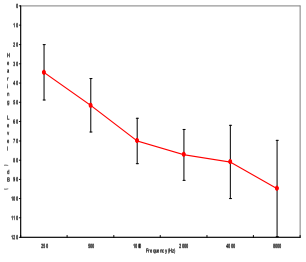


Fig 4: Mean pure tone thresholds (air conduction)N=85. Error bars represent the range

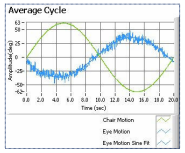
USHER TYPE III

Only two Usher families had mutations in USH3 gene and are being evaluated for objective evidence of progression of hearing impairment.

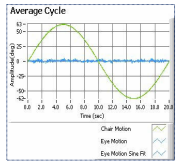
Results of Vestibular function testing

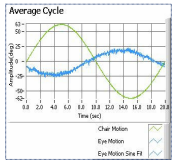
USHER TYPE I

Contrary to expected findings, three subjects (Mr Pt2, MsPt3 and Mr Pt1 exhibited good vestibular function in spite of mutations in USH1B and USH1C genes respectively. 21 subjects with mutations in USH1 genes had absent peripheral vestibular function (as demonstrated by rotational and or caloric tests).



Figures 5,6, 7 Computer print out of sinusoidal rotation Fig 5 (left) – normal. Fig 6 (bottom left)– Response of a classical Usher type I subject Fig 7(bottom right)- Normal vestibular function of Mr Pt1

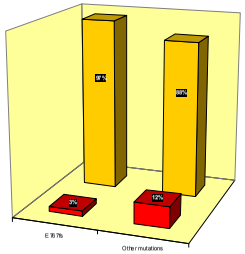




USHER TYPE II

38 subjects had a frameshift mutation (E767fs) in USH2A gene which has been previously reported to cause phenotypic variability.[6] Our cohort with this mutation had normal vestibular function on rotational testing, and a lower incidence of canal paresis (only one subject with 22% CP) when compared with other mutations within the USH2A gene.

Fig 8: Bar chart comparing canal paresis in those with E767fs mutations vs other mutations in USH2A gene. Results obtained by bithermal caloric tests)



CONCLUSION

This study confirms the phenotypic heterogeneity in Usher syndrome. While some mutations in USH1C and USH1B appear to predispose to an atypical audiovestibular phenotype, the more frequent E767fs mutation in USH2A was associated with normal vestibular function in our study population. Further clarification of the phenotypic-genotypic correlation will be possible once audiovestibular and genetic analyses are completed

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sense for deafblind people

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