LETTER TO JMG

Distinctive audiometric features between USH2A and USH2B subtypes of Usher syndrome

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Usher syndrome (USH) is an autosomal recessive disorder characterized by hearing impairment and retinitis pigmentosa (RP). The prevalence of USH varies from one population to another, for example, 3.4-4.4 per 100,000 in Scandinavian and North American populations1,2 and 6.2-10 per 100,000 in the city of Birmingham, UK.3 This syndrome is clinically heterogeneous and three clinical forms have been described: (1) USH type I (USH1) is characterized by severe to profound congenital deafness, constant vestibular dysfunction, and prepubertal onset of RP; (2) USH type II (USH2) is characterized by congenital moderate to severe deafness, absence of vestibular dysfunction, and onset of RP usually in the late second to early third decade; (3) USH type III (USH3) is characterized by postlingual progressive deafness, occasional vestibular dysfunction, and progressive RP with a variable age of onset (see also http://www.ncbi.nlm.nih.gov/omim). Usher syndrome is also genetically heterogeneous; at least six distinct loci are responsible for USH1 (USH1A-F), three for USH2 (USH2A-C), and one for USH3 (Hereditary hearing loss homepage at URL http://dnalab.www.uia.ac.be/dnalab/hhh).

Usher syndrome type II (USH2) appears to be the commonest clinical form of the disorder in the American population, accounting for more than 50% of all USH cases.4 This clinical form tends to be rare in other populations.7 In the Tunisian population, only two USH2 families, Us and Z (this work), have been identified so far. These families were ascertained from villages from the south and the north of Tunisia, respectively, where endogamous marriage is relatively common for social and cultural reasons. Of all the USH2 subtypes, USH2A seems to be the most frequent. According to a study performed in various ethnic populations, USH2A is responsible for more than 85% of USH2 cases.5 This genetic form showed considerable phenotypic heterogeneity. Indeed, mutations in the USH2A gene were found in patients presenting with an atypical USH2 phenotype, including progressive hearing loss, variable vestibular dysfunction, and RP.6 USH2A mutations were also identified in patients with recessive RP without hearing loss.7

So far, no distinctive clinical features have been observed between the six USH1 subtypes.8 However, phenotypic heterogeneity has been reported for the USH2A and USH2C subtypes.9 These findings prompted us to perform a thorough clinical and audiological analysis in USH2 Tunisian families, searching for clinical differences between the USH2A and USH2B subtypes of the Usher type II syndrome.

MATERIALS AND METHODS

In this study, the Z family affected with USH2 was examined. A complete medical examination and history was undertaken with a general examination and systematic search for signs suggestive of a syndromic form of hearing impairment. All family members underwent detailed audiological, ophthalmological, and electrophysiological testing. Air conduction pure tone average (ACPTA) threshold in the conversational frequencies (0.25, 0.5, 1, and 2 kHz) was calculated for each ear and was used to define the severity of the hearing loss according to the better hearing ear: mild (25 dB < ACPTA ≤ 39 dB), moderate (40 dB ≤ ACPTA ≤ 69 dB), severe (70 dB ≤ ACPTA ≤ 89 dB), and profound (ACPTA ≥ 90 dB). The establishment of RP required that at least one family member had a history of night blindness, progressive reduction of peripheral vision, diminished or absent electroretinogram, and a typical fundoscopy appearance of the retina. In addition, bilateral vestibular function was investigated by calorics stimulation. The statistical significance of the threshold value differences measured in Us and Z patients was assessed using the Student-Fisher test (t-test).

Genetic subtypes of USH2 syndrome were determined by linkage analysis. Family Us has been previously studied.4 For family Z, genomic DNA was extracted according to standard protocols. Genotype analysis was carried out as previously described10 using polymorphic microsatellite markers corresponding to the USH2A locus.10 Linkage analysis was performed using the LINKAGE 5.1 program package.11 Two point lod scores were calculated with the MLINK program of the FASTLINK package. USH2 syndrome was assumed to be inherited in a recessive manner and coded as fully penetrant with a disease allele frequency estimated to be 10-4. The allele frequencies of the polymorphic markers and the meiotic recombination frequencies for males and females were assumed to be equal.

RESULTS

A total of 36 subjects, including 14 affected with USH2 (seven from family Us and seven from family Z), were examined. Family Us patients have a moderate to severe sensorineural bilateral hearing loss.7 Audiometry tests performed in family Z patients showed a moderate to profound bilateral sensorineural hearing loss. Ophthalmological examinations detected RP in the patients from both families, with the appearance of night blindness occurring in the first or second decade for Us family members. No vestibular dysfunction was detected in the patients of either family using the calorics test, nor was there any history of a delay in the age of walking. All heterozygous carriers exhibited normal results for the audiological and opthalmological examination. However, two subjects (III.4 and III.7) from family Z (fig 1) showed mild hearing loss caused by unilateral otosclerosis and bilateral presbyacusis. No other abnormalities were observed in these two subjects. On the whole, the clinical signs observed in affected subjects from these two families were indicative of a typical form of USH2.

Abbreviations: USH, Usher syndrome; RP, retinitis pigmentosa; ACPTA, air conduction pure tone average
Family Us has been reported to be linked to the USH2B locus. For family Z, we started the genetic analysis by testing the involvement of the USH2A locus. Haplotype and linkage analysis showed that all affected subjects were homozygous for the three microsatellite markers D1S237, D1S474, D1S229 (fig 1). A maximum lod score of 3.54 ($\theta=0.00$) was obtained for the most informative marker D1S237. Mutation analysis of the *Usherin* gene in family Z shows a novel frameshift mutation, 2212delA, after amino acid R737.

**DISCUSSION**

In order to identify the clinical parameters distinguishing the two USH2 subtypes, we analysed the clinical results of both families. Phenotypic heterogeneity has been reported in USH2A and USH2C subtypes and ophthalmological differences in the onset of RP have been observed. In our study, the patients from the two families showed a difference in the onset of the RP suggesting that the USH2A form may be more severe than USH2B. In addition, in both families, no progression of hearing loss has been detected and thresholds were stable for more than 14 years (data not shown). This stability in deafness is in agreement with the clinical features reported in 1999 by Fagerheim et al in two isolated populations. Nevertheless, a progression of the hearing impairment in USH2A patients younger than 40 years from The Netherlands.

- Usher syndrome type II (USH2) is an autosomal recessive disorder characterised by congenital moderate to severe sensorineural hearing loss and progressive retinitis pigmentosa which appears in the late second to early third decade. Three loci responsible for this clinical form, USH2A, USH2B, and USH2C, have been mapped to chromosomes 1, 3, and 5, respectively.
- Two large consanguineous families Z and Us affected with USH2 syndrome were recruited from northern and southern Tunisia, respectively. Patients showed congenital, non-progressive, moderate-severe to profound hearing loss associated with progressive retinitis pigmentosa.
- In family Z, linkage analysis showed cosegregation of Usher syndrome with the USH2A locus. A maximum lod score of 3.54 at $\theta=0.00$ was obtained for the most informative marker, D1S237. Family Us has previously been reported to be linked to the USH2B locus.
- To evaluate hearing impairment in the two USH2A and USH2B subtypes, we analysed the clinical results and found distinctive audiometric and ophthalmological features that might be of interest to distinguish between these two USH2 subtypes.
has been detected and estimated to be 0.7 dB/year on average for frequencies 0.25 to 4 kHz. Furthermore, distinctive audiometric features for all frequencies were observed in the two USH2 families. We have noted at the low frequencies (0.25, 0.5, and 1 kHz) a hearing loss which ranged from mild to moderate in family Us and from moderate to severe in family Z. However, hearing loss tends to be severe at the high frequencies in the two families (fig 2). A comparison of mean threshold values measured for all affected subjects of the two subtypes was performed using the t test. A significant difference was obtained for the right and left ear at low frequencies (p<0.05).

This finding may give rise to a simple method to distinguish the two USH2 subtypes, which is the audiometric test. However, the recruitment of other USH2 families is needed to confirm and corroborate this phenotypic difference between USH2A and USH2B.

ACKNOWLEDGEMENTS

We thank the members of the two families for their participation in this study, Dr André Mégarbané and Jean Pierre Hardelin for their critical reading of the manuscript, and Dr Ahmed Rebaii for assistance with the statistical analysis. The work was supported by Secrétariat d’État à la Recherche Scientifique et à la Technologie (Tunisia) and The Foundation Fighting Blindness and NIDCD P01-DO01813 S (USA).

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*J Med Genet* 2002 39: 281-283
doi: 10.1136/jmg.39.4.281

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