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Report

Genetic Heterogeneity of Usher Syndrome: Analysis of 151 Families with Usher Type I

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Usher syndrome type I is an autosomal recessive disorder marked by hearing loss, vestibular areflexia, and retinitis pigmentosa. Six Usher I genetic subtypes at loci USH1A–USH1F have been reported. The *MYO7A* gene is responsible for USH1B, the most common subtype. In our analysis, 151 families with Usher I were screened by linkage and mutation analysis. *MYO7A* mutations were identified in 64 families with Usher I. Of the remaining 87 families, who were negative for *MYO7A* mutations, 54 were informative for linkage analysis and were screened with the remaining USH1 loci markers. Results of linkage and heterogeneity analyses showed no evidence of Usher types Ia or Ie. However, one maximum LOD score was observed lying within the USH1D region. Two lesser peak LOD scores were observed outside and between the putative regions for USH1D and USH1F, on chromosome 10. A HOMOG $\chi^2_{(1)}$ plot shows evidence of heterogeneity across the USH1D, USH1F, and intervening regions. These results provide conclusive evidence that the second-most-common subtype of Usher I is due to genes on chromosome 10, and they confirm the existence of one Usher I gene in the previously defined USH1D region, as well as providing evidence for a second, and possibly a third, gene in the 10p/q region.

Usher syndrome is defined as congenital neurosensory hearing loss with retinitis pigmentosa (RP). Its frequency is estimated to be 3.5/100,000 in Scandinavia (Hallgren 1959; Nuutila 1970; Grondahl 1987) and 4.4/100,000 in the United States (Boughman et al. 1983). Although relatively rare, Usher syndrome has been estimated to account for 50% of all individuals who are both deaf and blind and for ~3%–6% of all children who are deaf (Vernon 1969).

Usher syndrome is both clinically and genetically heterogeneous. Clinical heterogeneity is demonstrated by the variation in the severity and progression of the hearing impairment, the age at onset of retinal degeneration, and the presence or absence of vestibular areflexia. There are three clinical types of Usher syndrome. Usher type I is the most severe subtype, characterized by congenital profound deafness, early-onset RP (usually diagnosed before puberty), and absent or severely diminished vestibular responses. Usher type II is marked by a congenital moderate-to-severe hearing impairment that is identified by a characteristic sloping audiogram, a later diagnosis of RP (during the 2d decade of life), and normal vestibular responses. Usher type III is characterized by a progressive hearing loss, with variable RP and progressive vestibular dysfunction (Kimberling and Moller 1995; Smith et al. 1995). Types I and II are the most common forms of Usher syndrome.

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Table 1

Summary of the Clinical and Genetic Subtypes of the Usher Syndromes

Usher Type[a] and Location	Gene	Screening Markers[b]
I		
USH1A-14q32		D14S78, D14S250, D14S292, D14S260
USH1B-11q13.5	*MYO7A*	D11S527, D11S4186, D11S906, D11S911
USH1C-11p15.1	*USH1C*	D11S921, D11S902, D11S4160, D11S899
USH1D-10q21-22		D10S529, D10S195, D10S202, D10S573
USH1E-21q21		D21S1905, D21S1914, D21S269, D21S1913
USH1F-10		D10S193, D10S1791, D10S220, D10S1790
II		
USH2A-1q41[c]	*USH2A*	D1S237, AFM143, AFM144, D1S490
USH2B-3p		
USH-5q[c]		D5S617, D5S484, D5S505, D5S485
III		
USH3-3q21-25		D3S1555, D3S1308, D3S1279, D3S1280

[a] Phenotypes are described in the text.
[b] Markers typed for linkage analysis in the present study.
[c] Families were tested for linkage for Usher II and III markers. The results were negative and are not reported here.

At least 10 loci have been identified for Usher syndrome: 6 for Usher type I (USH1A–USH1F), 3 for Usher type II (USH2A–USH2C) and 1 for Usher type III (Kimberling et al. 1990, 1992; Kaplan et al. 1992; Smith et al. 1992; Sankila et al. 1995; Wayne et al. 1996, 1997; Chaib et al. 1997; Hmani et al. 1999; Pieke-Dahl et al. 2000) (table 1). The most common form of Usher type I, Ib, is localized to 11q13.5 (locus USH1B [MIM 276903]). The other five loci are believed to be uncommon: the gene for Usher type Ia maps to 14q32 and has been observed in families with ancestry from the Poitou-Charentes region of France (Kaplan et al. 1992); type Ic maps to 11p15.1 and has been reported in the French Acadian population (Smith et al. 1992); type Ie has been mapped to 21q21 by homozygosity mapping in a Moroccan family (Chaib et al. 1997); and types Id and If both map to chromosome 10 and have been identified in single Pakistani (Id) and Hutterite (If) families, respectively (Wayne et al. 1996, 1997). Usher syndrome type II is known to have at least three loci, and there is evidence for an additional, as yet unlocalized, subtype (Pieke-Dahl et al. 2000). Usher type IIa is the most common of the milder forms of Usher syndrome and maps to 1q41 (Kimberling et al. 1990). Type IIb maps to chromosome 3p23-24.2 (Hmani et al. 1999), and Usher type IIc maps to 5q14.3-21.3 (Pieke-Dahl et al. 2000). There is only one Usher III locus, USH3, mapping to 3q21-25 (Sankila et al. 1995). Families reported to have Usher type III are primarily of Finnish origin; however, there are reports of one Italian family (Gasparini et al. 1998) and two Spanish families that showed linkage to the 3q region (Espinos et al. 1998).

Table 2

Distribution of *MYO7A* Mutations in 169 Families with Usher Syndrome

Usher Phenotype(s)	Mutation	Linkage Informative?	No.
I	MYO7A$^+$	Yes	46
I	MYO7A$^+$	No	18
I	MYO7A$^-$	Yes	54
I	MYO7A$^-$	No	33
II and III	MYO7A$^-$	No	18
Total			169

NOTE.—Families are divided by phenotype, the presence or absence of at least one pathologic *MYO7A* mutation, and informativeness. MYO7A$^+$ represents 64 families with Usher I with at least one identifiable *MYO7A* mutation; only 46 of these families are informative for linkage. The remaining families revealed no mutation (MYO7A$^-$). The analysis reported here has focused on the 54 MYO7A$^-$ families with Usher I that were informative for linkage analysis.

For the 10 known Usher loci, 3 genes have been identified. *MYO7A* is responsible for Usher Ib; *USH2A* is a novel gene, responsible for Usher IIa, that codes for a protein now called "usherin"; and the third gene, *USH1C*, which codes for a PDZ (PSD95, Dlg, ZO-1) domain–containing protein named "harmonin," has been recently identified (Verpy et al. 2000; Bitner-Glindzicz et al. 2000). Mutations in *MYO7A* have been found to account for ~60% of all Usher I cases (W.J.K., unpublished data). Although a wide spectrum of mutations in the *MYO7A* gene have been described in patients with Usher Ib, the gene has also been shown to harbor mutations producing nonsyndromic deafness, including DFNA11 and DFNB2, as well as atypical Usher syndrome with progressive hearing loss (Levy et al. 1997; Liu et al. 1997*a*, 1997*b*, 1998).

Here we report the results of linkage and mutation analysis of 169 families with Usher that represent diverse backgrounds from the United States, Europe, Colombia, and South Africa. Our results show that one or more

Table 3

Summary of Heterogeneity Analysis of 54 Families with Usher Type I

Usher Subtype	Marker Set	α	Heterogeneity χ^2
IA	14q	.05	.11
IB	11q	.15	3.98[a]
IC	11p	.15	4.15[a]
ID/IF	10	.75	36.30[a]
IE	21q	.05	.81

NOTE.—Heterogeneity analysis was performed with the HOMOG program using markers spanning each of the USHI loci.

[a] Significant, providing evidence for presence of subtypes.

genes on chromosome 10 are responsible for a majority of the families with Usher I that is not linked to *MYO7A* (*MYO7A*$^-$).

We studied 169 independent families, including 242 affected individuals, with Usher syndrome. Of these families, 151 had Usher I, 12 had Usher II, and 6 had Usher III (table 2). The results for Usher types II and III will be reported elsewhere. Sixteen families with Usher I were consanguineous. The families were collected in the United States (86 families), The Netherlands (37 families), Sweden (31 families), South Africa (5 families), Spain (4 families), Colombia (3 families), and England (3 families); however, the ethnic composition is primarily of European extraction. The five South African and three Colombian families were of European ancestry. The sample group also included two French Acadian families who showed linkage to the USH1C region.

All families were assigned to a specific subtype of Usher syndrome on the basis of the pattern and severity of hearing loss, the presence or absence of vestibular areflexia, and the presence of RP. The clinical diagnosis was determined from the patient's medical history and results of audiometric, ophthalmologic, and vestibular examinations. The human-subjects committee at each location approved this study, and written, informed consent was obtained from all participants.

Blood samples were collected, and genomic DNA was extracted using a Puregene kit (Gentra Systems). Fluorescent (6-FAM, TET, or HEX) oligonucleotide primers were used to amplify polymorphic markers surrounding the various Usher loci (for the specific markers that were typed, see table 1). Markers were amplified according to the following protocol: 95°C for 5 min, 30 cycles (94°C for 1 min, 60°C for 1 min, and 72°C for 1 min) and 60°C for 30 min. PCR products were then pooled, denatured, and separated on 4.25% polyacrylamide gels in an ABI 377 automated sequencer (PE Biosystems), and fragment analysis was performed using GENESCAN 2.1 software. Genotyping data were collected and were analyzed using GENOTYPER 2.0.

All families with Usher I in the present report had been subjects of a previous report on a mutation screen of 14 exons (Weston et al. 1996). However, the mutation analysis in the present report involved screening 46 of the 48 coding exons for all 169 families in our sample. A summary of the mutations observed is available on the GeneClinics home page, and a report on these mutations will be published elsewhere.

Linkage analysis of DNA markers was performed using the LINKAGE programs (Lathrop et al. 1985). Two-point and multipoint analyses were computed for all 54 families with *MYO7A*$^-$ Usher syndrome. Rolling multipoint analysis across the entire span of chromosome 10 markers generated LOD scores by comparison of overlapping sets of four contiguous marker loci with the test locus (five-point analysis). The pattern of inheritance of Usher syndrome was assumed to be recessive with full penetrance for the mutant homozygote. Gene frequency of the mutant allele was set at .001. The number of alleles was taken from information in the Whitehead Institute for Biomedical Research/MIT Center for Genome Research home page and the The Genome Database home page. The frequencies of the marker alleles were assumed to be equal. Heterogeneity analysis was done using the rolling multipoint LOD scores, generated as outlined above, with HOMOG, version 2.4.

Of the 169 families initially studied, 151 had Usher type I. Of the families with Usher I, 64 had at least one detectable *MYO7A* mutation. Of the families with *MYO7A*$^-$ Usher I, 54 were informative for linkage and were analyzed using the LINKAGE and HOMOG computer programs. These 54 families were screened with flanking markers, as summarized in table 1, for all known USH1 loci. Both two-point and rolling multipoint analyses were performed on all families, using all USH1 loci. Except for chromosome 10 markers, none of the LOD scores were significantly positive—that is,

Table 4

Results of Two-Point Analysis, on Chromosome 10, for 54 Families with Usher Type I

	Two-Point LOD Score at θ =					
Marker	0	.05	.1	.2	.3	.4
D10S193	−∞	−8.648	−3.316	.019	.527	.264
D10S1791	−∞	−3.962	−.213	1.487	1.130	.411
D10S220	−∞	−4.106	−.375	1.378	.999	.278
D10S1784	−∞	.147	.120	.072	.033	.009
D10S1790	−∞	−3.245	.099	1.545	1.027	.240
D10S1756	−∞	−.652	.680	1.115	.723	.240
D10S1743	−∞	3.097	4.210	3.517	1.918	.560
D10S1665	−∞	.669	2.219	2.106	1.136	.259
D10S529	−∞	3.970	5.268[a]	4.297	2.339	.629
D10S195	−∞	1.859	4.219	4.175	2.494	.802
D10S202	−∞	1.050	3.142	3.198	1.916	.621
D10S573	−∞	−3.035	.261	1.658	1.138	.338

[a] Highest two-point LOD score.

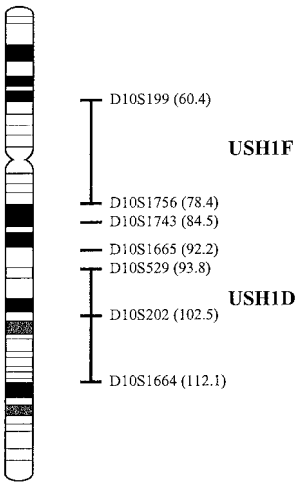

Figure 1 Map of chromosome 10. The critical regions of USH1D and USH1F are outlined, and the markers used in the linkage analysis are listed, with their position (in cM) from the p-arm telomere.

there was no evidence for linkage outside chromosome 10. All sets of scores generated from the rolling multipoint analysis were used for a multiple HOMOG analysis. Table 3 summarizes the results of the HOMOG analyses for each Usher locus. The χ^2 values of 0.81 and 0.11 are clearly not significant, providing no evidence for the presence of either USH1A or USH1E in this sample. However, the $\chi^2_{(1)}$ values of 3.98, 4.15, and 36.30 suggest the presence of a mixture of USH1B, USH1C, USH1D, or USH1D/USH1F within the 54 families.

Two French Acadian families were included in the

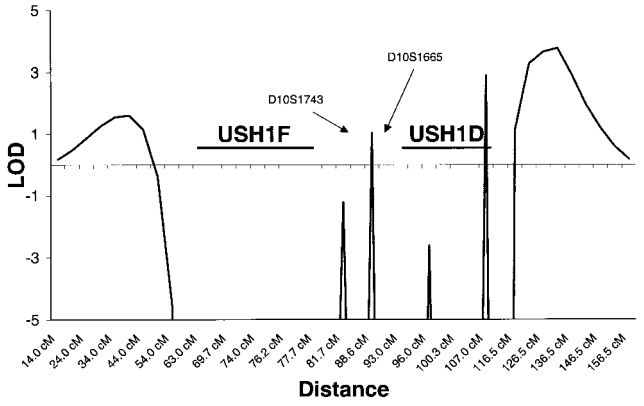

Figure 2 Map of multipoint LOD scores for chromosome 10 markers and the families with *MYO7A*$^-$ Usher I: results of chromosome 10 multipoint analysis for all families, with the exclusion of the three 11q-linked and two French Acadian families. A LOD score of 1.03 lies between markers D10S1743 and D10S1665 between the two defined regions of USH1D and USH1F, and a LOD score of 2.89 lies within the USH1D region. Additional LOD scores, of 1.60 and 3.77, lie outside the regions of USH1F and USH1D, respectively.

MYO7A screening to test the possibility of a digenic effect involving the *MYO7A* gene; however, no mutations were detected. The sensitivity of the HOMOG program is demonstrated by the detection of linkage heterogeneity as a result of the inclusion of these two families. In addition, we identified three families that each had LOD scores >2.0 for 11q markers. We believe that these families have *MYO7A* mutations that were not detectable by our testing strategy. When these five families were removed from the analysis, the significant $\chi^2_{(1)}$ HOMOG values for USH1B and USH1C disappeared.

The highly significant $\chi^2_{(1)}$ value of 36.30 for chromosome 10 markers prompted us to further examine the USH1D and USH1F regions. The USH1D and USH1F loci have been mapped to chromosomal locations 10q21.22 and 10pq (fig. 1). The broad critical regions and close proximity of these two loci to each other necessitated the selection of 12 chromosome 10 markers spanning both critical regions, as well as the intervening space, covering a distance of ~50 cM. These markers were used in two-point and rolling multipoint analyses. Table 4 shows the results of the two-point analysis for the individual markers, for USHID/USH1F. The highest LOD score, 5.27, was obtained for marker D10S529 at $\theta = .10$.

Multipoint analysis of the non-USH1B families, with the exclusion of the two families of French Acadian ancestry and of three families with 11q linkage, resulted in one significant maximum LOD score (Z_{max}), 3.77, lying on the qter side, just beyond the USH1D critical region. In addition, a LOD of 1.03 was observed between markers D10S1743 and D10S1665, which is between the two previously defined critical regions of USH1D and USH1F. In addition, a Z_{max} of 2.89 also lies within the USH1D region. Interestingly, the analysis also provided a LOD score of 1.60 just pter of the putative region of USH1F (fig. 2). On the surface, these results do not support the hypothesis of an Usher gene in the USH1F region. However, the impact that heterogeneity due to linked genes has on LOD scores is not well understood; and it is conceivable that a mixture of families that are heterogeneous because of linked genes could yield a LOD-score distribution with maxima that are shifted from the true location of the genes actually responsible. We had expected to see bimodality in the heterogeneity $\chi^2_{(1)}$ but found only a single maximum corresponding to the presence of an USH1D locus (fig. 3). It may be that Usher If is not frequent and that there are too few families in our sample for the second maximum to be detected. An alternative explanation is that USH1F is incorrectly mapped and that it actually lies between markers D10S1743 and D10S1665 or that there is another Usher I gene lying between USH1D and USH1F.

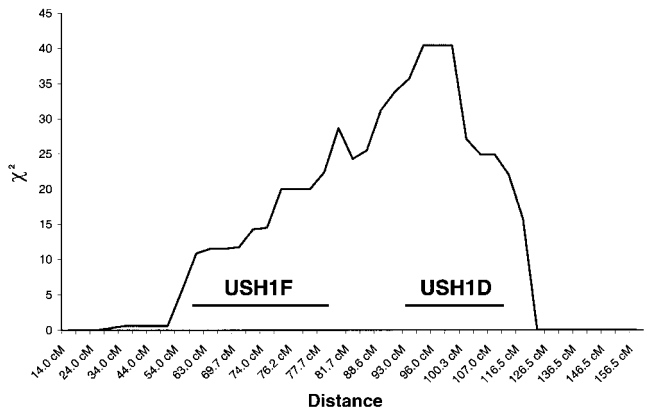

Figure 3 Plot of chromosome 10 HOMOG analysis. Rolling χ^2 values generated from the chromosome 10 multipoint analyses (data from fig. 2) are plotted against position (in cM). A maximum χ^2 of 40.44 lies in USH1D and a second, lesser χ^2 value of 28.71 lies just outside the USH1F region.

These data provide an initial estimate of the proportion of the various Usher type I subtypes. Our original sample of 169 families with Usher syndrome was subdivided on the basis of the presence or absence of a *MYO7A* mutation. After the exclusion of the 18 families with Usher II and Usher III and of the 51 families with non–linkage-informative Usher I, the remaining sample consisted of 100 families with linkage-informative Usher I (table 2). Forty-six families, representing 46% of the group with linkage-informative Usher I, had a pathologic *MYO7A* mutation. The remaining 54 families with Usher I did not have an identified mutation. These families represented 54% of our sample. From our analysis of families with *MYO7A*$^-$ Usher I, the proportion of individuals with Usher type Ic in our sample is estimated at 2%. The estimate for Usher Ic is obviously biased, because the two families were purposefully included in the analyses. In addition, the three families with Usher 1b linked to 11q constitute ~3% of the sample. Thus, in our sample, 49% of families with Usher I had a predicted or confirmed *MYO7A* mutation (i.e., Usher Ib). Of the remaining families, 33 lacking the *MYO7A* link to the USH1D and USH1F regions constitute 61% of the *MYO7A*$^-$ sample, or 33% of all families with linkage-informative Usher I. The remaining individuals with Usher I are unconfirmed for linkage to any of the six Usher I loci, and they constitute 16% of the sample.

The findings presented here have important implications for characterizing and defining the heterogeneity of Usher syndrome type I. These results support the genetic heterogeneity of Usher syndrome and also indicate for the first time that USH1D/USH1F is the second-most-common Usher I subtype.

The genetic heterogeneity of Usher syndrome type I is complex and raises the question of clinical differentiation. Our clinical findings have not yet suggested any obvious clinical variance between these subgroups. However, deeper and more-extensive examinations of the audiologic, vestibular, and retinal phenotypes may reveal differences that, because of heterogeneity, had not previously been noticed. Consequently, our next efforts will focus on the use of both clinical and genetic factors to differentiate, characterize, and further define the heterogeneity of the Usher I subtypes.

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

GeneClinics, http://www.geneclinics.com
Genome Database, The, http://www.gdb.org
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *MYO7A* [MIM 276903])
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www.genome.wi.mit.edu

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