Short reports

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Evidence for a fourth locus in Usher syndrome type I

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Abstract

Usher syndrome type I (US1) is an autosomal recessive condition in which three different genes have been already localised (USH1A, USH1B, and USH1C on chromosomes 14q32, 11q13, and 11p15 respectively). The genetic heterogeneity of US1 has been confirmed in a previous study by linkage analysis of 20 French pedigrees. Here, we report the genetic exclusion of the three previously reported loci in two large multiplex families of Moroccan and Pakistani origin, suggesting the existence of at least a fourth locus in Usher syndrome type I.

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Key words: Usher syndrome type I; fourth locus.

Usher syndrome type I is an autosomal recessive disorder characterised by profound con-

genital hearing impairment with unintelligible speech, early retinitis pigmentosa, and constant vestibular dysfunction.¹ Three different loci have so far been localised by linkage analysis in informative families (USH1A, USH1B, and USH1C). USH1A has been mapped to chromosome 14q32.1-14q32.3 in nine French families from the Poitou region suggesting a founder effect.² USH1B has been mapped to chromosome 11q13.5 in 27 families from the United States, Sweden, Ireland, and South Africa³ and USH1C has been mapped to chromosome 11p15.1 in eight French Acadian families.⁴ In 1994, we provided evidence for genetic heterogeneity of Usher syndrome type I in 20 French pedigrees by showing that families unlinked to chromosome 14q32 were either linked to chromosome 11q or consistent with linkage to chromosome 11p.⁵ Here, we report the genetic exclusion of the three previously reported loci in two families of Moroccan and

Figure 1 Exclusion of the Usher syndrome type I gene from chromosomes 14q32(A), 11q13(B), and 11p15(C) in both families.

Pairwise lod score values for polymorphic markers of chromosome 14q, 11q, and 11p

Locus (probe)	Families	Recombination fractions						Z	θ
		0	0.01	0.05	0.10	0.20	0.30		
<i>Chromosome 14q</i>									
D14S51 (mfd165)	Fam 1	−0.63	−0.55	−0.35	−0.22	−0.09	−0.04	0	0.50
	Fam 2	−∞	−5.73	−2.98	−1.84	−0.81	−0.31	0	0.50
	Total	−∞	−6.28	−3.33	−2.06	−0.90	−0.35	0	0.50
D14S78 (AFM234we5)	Fam 1	−∞	−3.47	−1.88	−1.16	−0.50	−0.19	0	0.50
	Fam 2	−0.37	−0.67	0.15	0.26	0.25	0.13	0.26	0.10
	Total	−∞	−3.64	−1.73	−0.89	−0.25	−0.06	0	0.50
D14S13 (MLJ14)	Fam 1	−∞	−1.54	−0.81	−0.32	−0.20	−0.07	0	0.50
	Fam 2	−∞	−4.87	−2.44	−0.91	−0.58	−0.21	0	0.50
	Total	−∞	−6.41	−3.25	−1.93	−0.78	−0.28	0	0.50
D14S260 (AFM238we7)	Fam 1	−∞	−2.54	−1.27	−0.80	−0.38	−0.16	0	0.50
	Fam 2	−∞	−2.70	−1.36	−0.82	−0.36	−0.14	0	0.50
	Total	−∞	−5.24	−2.63	−1.62	−0.74	−0.30	0	0.50
<i>Chromosome 11q</i>									
D11S903 (AFM077xel)	Fam 1	−∞	−1.91	−0.89	−0.55	−0.23	−0.09	0	0.50
	Fam 2	−∞	−1.65	−0.87	−0.45	−0.15	−0.05	0	0.50
	Total	−∞	−3.56	−1.76	−1.00	−0.38	−0.14	0	0.50
D11S913 (AFM164zf12)	Fam 1	−∞	−1.43	−0.75	−0.47	−0.21	−0.08	0	0.50
	Fam 2	−∞	−4.93	−2.51	−1.50	−0.63	−0.25	0	0.50
	Total	−∞	−6.36	−3.26	−1.97	−0.84	−0.33	0	0.50
D11S916 (AFM185yal)	Fam 1	−∞	−1.50	−0.71	−0.42	−0.21	−0.10	0	0.50
	Fam 2	−∞	−4.92	−2.51	−1.50	−0.63	−0.25	0	0.50
	Total	−∞	−6.42	−3.22	−1.92	−0.84	−0.35	0	0.50
D11S527 (zd5)	Fam 1	−∞	−1.60	−0.85	−0.53	−0.22	−0.08	0	0.50
	Fam 2	−∞	−4.93	−2.51	−1.50	−0.63	−0.25	0	0.50
	Total	−∞	−6.53	−3.36	−2.03	−0.85	−0.33	0	0.50
D11S937 (AFM256zb5)	Fam 1	−∞	−1.48	−0.67	−0.36	−0.13	−0.05	0	0.50
	Fam 2	−∞	−5.66	−2.93	−1.80	−0.79	−0.31	0	0.50
	Total	−∞	−7.14	−3.60	−2.16	−0.92	−0.36	0	0.50
<i>Chromosome 11p</i>									
D11S419 (Mfd58)	Fam 1	−∞	−1.65	−0.89	−0.55	−0.23	−0.09	0	0.50
	Fam 2	−1.22	−0.96	−0.54	−0.32	−0.13	−0.05	0	0.50
	Total	−∞	−2.61	−1.43	−0.87	−0.36	−0.14	0	0.50
D11S899 (AFM022th2)	Fam 1	−∞	−3.40	−1.76	−1.07	−0.46	−0.18	0	0.50
	Fam 2	−∞	−2.34	−1.06	−0.59	−0.22	−0.07	0	0.50
	Total	−∞	−5.74	−2.82	−1.66	−0.67	−0.25	0	0.50
D11S902 (AFM072yd3)	Fam 1	−∞	−2.54	−1.26	−0.79	−0.39	−0.17	0	0.50
	Fam 2	−0.47	−0.24	0.04	0.10	0.02	−0.03	0.10	0.10
	Total	−∞	−2.78	−1.21	−0.69	−0.37	−0.20	0	0.50

Pakistani ancestry and suggest the existence of a fourth locus in Usher syndrome type I.

Six affected subjects and eight healthy relatives belonging to two consanguineous families of Moroccan and Pakistani origin, respectively, were ascertained. The affected subjects fulfilled the inclusion criteria of Usher syndrome type I, that is (1) deafness and absence of spontaneous language discovered in the first 18 months of life; (2) evidence of retinitis pigmentosa, including extinction of electroretinogram (ERG) before 10 years of age when systematically looked for and consistently present within the first two decades; and (3) bilateral vestibular areflexia (caloric test and rotational tests²). Genotyping at the three Usher syndrome type I loci was carried out as previously described.²⁻⁴

The table shows that consistently negative pairwise lod score values were obtained for polymorphic markers of chromosomes 14q, 11q, and 11p. Multipoint linkage analyses showed a large exclusion area around USH1A, USH1B, USH1C (40, 45, and 30 cM respectively) (fig 1) and haplotype analyses confirmed the unambiguous exclusion of the three Usher syndrome type I loci (fig 2).

Usher syndrome has long been regarded as a clinically and genetically heterogeneous condition. Indeed, at least two genes account for the late onset form of the disease (Usher syndrome type II, chromosome 1q42,⁶ and an as yet unlocalised second locus,⁷ while at least four genes now account for Usher syndrome type I. This figure is not unusual in autosomal recessive retinal dystrophies. For example, despite its clinical homogeneity, the Bardet-Biedl syndrome is now known to be accounted for by at least five genes.⁸⁻¹²

By providing evidence of at least a fourth locus, the present study gives additional support to the genetic heterogeneity of Usher syndrome type I. This genetic heterogeneity hampers prenatal diagnosis of this severe condition in small pedigrees and makes the identification of the gene particularly difficult. Yet, the identification of the myosin VIIA gene as the USH1B gene will hopefully speed up the identification of the other Usher syndrome genes.¹³

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Figure 2 Segregation of marker alleles of chromosomes 14q(A), 11q(B), and 11p(C) in families 1 and 2.

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