Homozygosity mapping to the USH2A locus in two isolated populations

T Fagerheim, P Raeymaekers, J Merren, K Mani, G K Jha, L Baumbach, V Brox, E Breines, B E Holdø, A Holdø, L Tranebjærg

Abstract

Usher syndrome is a group of autosomal recessive disorders characterised by progressive visual loss from retinitis pigmentosa and moderate to severe sensorineural hearing loss. Usher syndrome is estimated to account for 6-10% of all congenital sensorineural hearing loss. A gene locus in Usher type II (USH2) families has been assigned to a small region on chromosome 1q41 called the UHS2A locus. We have investigated two families with Usher syndrome from different isolated populations. One family is a Norwegian Saami family and the second family is from the Cayman Islands. They both come from relatively isolated populations and are inbred families suitable for linkage analysis. A lod score of 3.09 and 7.65 at zero recombination was reached respectively in the two families with two point linkage analysis to the USH2A locus on 1q41. Additional homozygosity mapping of the affected subjects concluded with a candidate region of 6.1 Mb. This region spans the previously published candidate region in USH2A. Our study emphasises that the mapped gene for USH2 is also involved in patients from other populations and will have implications for future mutation analysis once the USH2A gene is cloned.

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Department of Medical Genetics, Regional Hospital of Tromsø, N-9038 Tromsø, Norway
T Fagerheim
V Brox
E Breines
L Tranebjærg

Neurogenetics Laboratory, Department of Biochemistry and Born Bunge Foundation, University of Antwerp (UIA), Belgium
P Raeymaekers

Cayman Island Health Service, Grand Cayman, Cayman Islands, British West Indies
J Merren
K Mani
G K Jha

Division of Genetics, Department of Pediatrics, University of Miami, Miami, USA
L Baumbach

Community of Evenes, Norway
B E Holdø

General Practitioner, Evenes, Norway
A Holdø

Correspondence to:
Professor Tranebjærg.

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Usher syndrome is divided into three types with different clinical symptoms. Recently, linkage analysis has shown a high degree of heterogeneity within these types. Six distinct loci for Usher type I have been mapped: USH1A at 14q,[1] USH1B at 11q,[2] USH1C at 11p,[3] USH1D at 10q,[4] USH1E at 21q21,[5] and recently USH1F to 10q.[6] Only one locus for Usher type II has been mapped to 1q41,[7 8] but there is evidence for a second type II locus as one large family has been reported not to be linked to 1q.[9] The third Usher syndrome type (USH3) was mapped to chromosome 3q in Finnish families.[10]

Here, we present the results of linkage analysis of two consanguineous Usher families from completely different, isolated populations. The Norwegian Saami Usher family was first clinically described by Grøndahl and Mjøen.[11] The Cayman Islands family is the first described Usher family from this isolated population. No data on the degree of consanguinity in the population have been published.

The pedigree of the Norwegian Saami family (family 1) is shown in fig 1.

The pedigree of the large family from the Cayman Islands, British West Indies (family 2), shown in fig 2, is of mixed African-Black and British origin.The Cayman Islands were previously isolated from the rest of the world, but this is no longer the situation.

The diagnosis of Usher syndrome in these two families was established by audiological and ophthalmological examination. Stable moderate hearing loss was present in all affected subjects from early school age and retinitis pigmentosa developed in the teenage years. There was no vestibular dysfunction. Even though clinical data suggested Usher type II in both families, possible linkage to USH1A, USH1B, USH1C, USH1D, and USH3 loci was investigated by means of polymorphic microsatellite markers from the Généthon maps.[12] Some additional markers were provided from the Nordic Marker Consortium (Dr Claes Wadelius, Uppsala, Sweden). Linkage was detected to the USH2A locus on chromosome 1q41 in both families, and an extended two point linkage analysis with a total of 10 markers at the USH2A locus resulted in a significant lod score for both families. Family 1 reached a maximum lod score of 3.09 (table 1A) for marker D1S2629 and the large family 2 had a maximum lod score of 7.65 (table 1B) for marker D1S505, both at zero recombination frequencies. By investigation of the haplotypes in the family members of the two families and the minimal overlapping region of homozygosity in the patients, the border of the candidate region could be established at D1S505 in the centromeric direction and at D1S229 in the telomeric direction. This results in a candidate region of 6.1 Mb (according to the Location Database: http://cedar.genetics.soton.ac.uk), which is in accordance with the previously published candidate region for USH2A.[13 14] As seen in fig 1, the patients in the Saami family were heterozygous for the more distal markers, which enabled us to set the candidate region. The patients from the Cayman Island (fig 2), however, were homozygous for all markers spanning the disease locus. This family gave a high lod score but the affected family members share a larger chromosomal region around the USH2A locus, and therefore did not narrow down the disease region.

The two families were screened with the same markers under the same conditions, and it was therefore possible to compare the haplo-

Table 1 Two point lod scores of chromosome 1q41 markers versus the USH2A gene in (A) family 1 and (B) family 2. Usher syndrome was assumed to be inherited as a fully penetrant autosomal recessive disorder with a gene frequency of 4.4:100 000 in family 1 and 3.0:100 000 in family 2. There was no significant effect on the lod scores using allele frequencies calculated from 25 normal subjects in each population compared with assuming equal marker allele frequencies

	Recombination fraction								
Marker	*0.00*	*0.01*	*0.05*	*0.1*	*0.2*	*0.3*	*0.4*	*θ*	*Zmax*
A									
D1S425	2.95	2.89	2.57	2.19	1.44	0.77	0.23	0.0	2.95
D1S505	−∞	0.18	0.85	0.99	0.81	0.47	0.14	0.1	0.99
D1S217	2.23	2.18	1.96	1.70	1.19	0.70	0.24	0.0	2.23
D1S2703	2.92	2.85	2.54	2.16	1.42	0.75	0.22	0.0	2.92
D1S237	2.24	2.19	1.97	1.71	1.19	0.69	0.23	0.0	2.24
D1S2629	3.09	3.02	2.71	2.34	1.60	0.89	0.29	0.0	3.09
D1S2646	2.94	2.86	2.56	2.17	1.43	0.76	0.22	0.0	2.94
D1S2827	0.78	0.75	0.65	0.53	0.30	0.14	0.04	0.0	0.78
D1S229	−0.30	−0.23	−0.06	0.03	0.06	0.03	0.01	0.2	0.06
D1S490	−0.32	−0.24	−0.07	0.01	0.05	0.03	0.00	0.2	0.05
B									
D1S425	2.73	2.67	2.42	2.11	1.50	0.92	0.42	0.0	2.73
D1S505	7.65	7.48	6.83	5.99	4.28	2.55	0.99	0.0	7.65
D1S217	7.21	7.06	6.42	5.63	4.00	2.38	0.90	0.0	7.21
D1S2703	7.53	7.37	6.72	5.89	4.20	2.51	0.96	0.0	7.53
D1S237	4.20	4.11	3.75	3.29	2.33	1.40	0.57	0.0	4.20
D1S2629	7.06	6.91	6.31	5.56	3.98	2.38	0.91	0.0	7.06
D1S2646	6.95	6.80	6.19	5.42	3.86	2.31	0.89	0.0	6.95
D1S2827	7.21	7.06	6.43	5.63	4.00	2.38	0.90	0.0	7.21
D1S229	6.83	6.69	6.10	5.37	3.85	2.30	0.88	0.0	6.83
D1S490	7.06	6.91	6.31	5.55	3.98	2.38	0.91	0.0	7.06

types between the families. As shown in figs 1 and 2 the patients in the two families do not share the same haplotype around the disease locus. This is not surprising since the families come from different isolated populations situated far apart. Families with Usher syndrome from the USA and Europe have previously been shown to be linked to the same region.[13 15] We have not been able to compare haplotypes for the homozygous markers with published USHIIA families, because the other results were published with allele numbers instead of allele sizes for the critical DNA markers. It will be very interesting to see, when the gene is

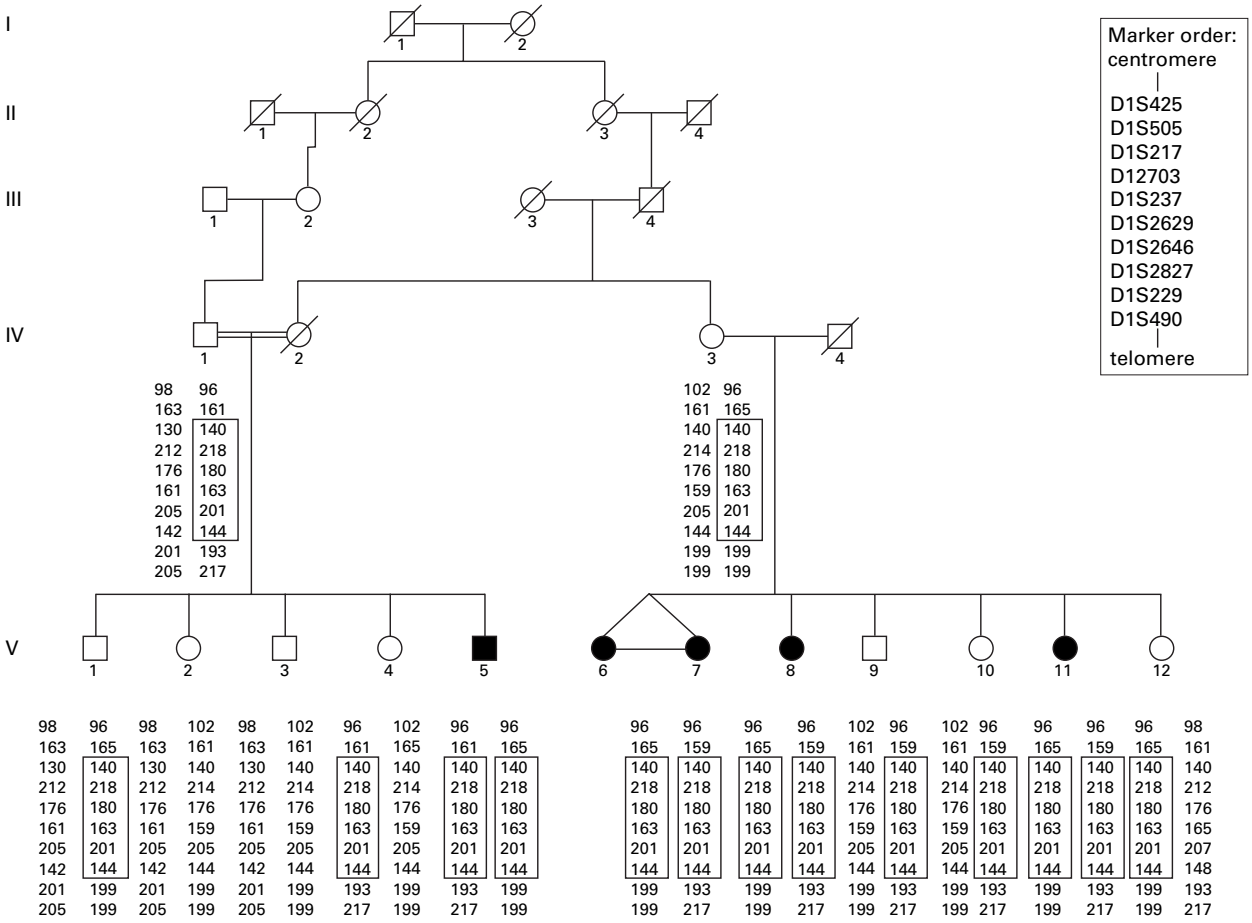

Figure 1 Pedigree of the Saami Usher family. The subjects shown with haplotypes were included in the linkage analysis. IV.6 and IV.7 are twins and had identical haplotypes, and are therefore counted as one person in the linkage analysis.

cloned, whether any of these families turn out to share haplotypes and possibly have the same mutations.

This is the first report of genetic investigation of Usher syndrome in a Saami family, and the population is not well studied for other diseases either. No further Saami Usher families were large enough for linkage analysis. So far, no data have appeared to clarify possible differences in disease gene frequencies between the Saami and the Norwegian populations. Along with future reports of the cloning of the USH2A gene, a mutation search in Saami families with Usher type II could be performed and the spectrum of mutations characterised. The study also represents the first step in characterising Norwegian Usher syndrome patients genetically.

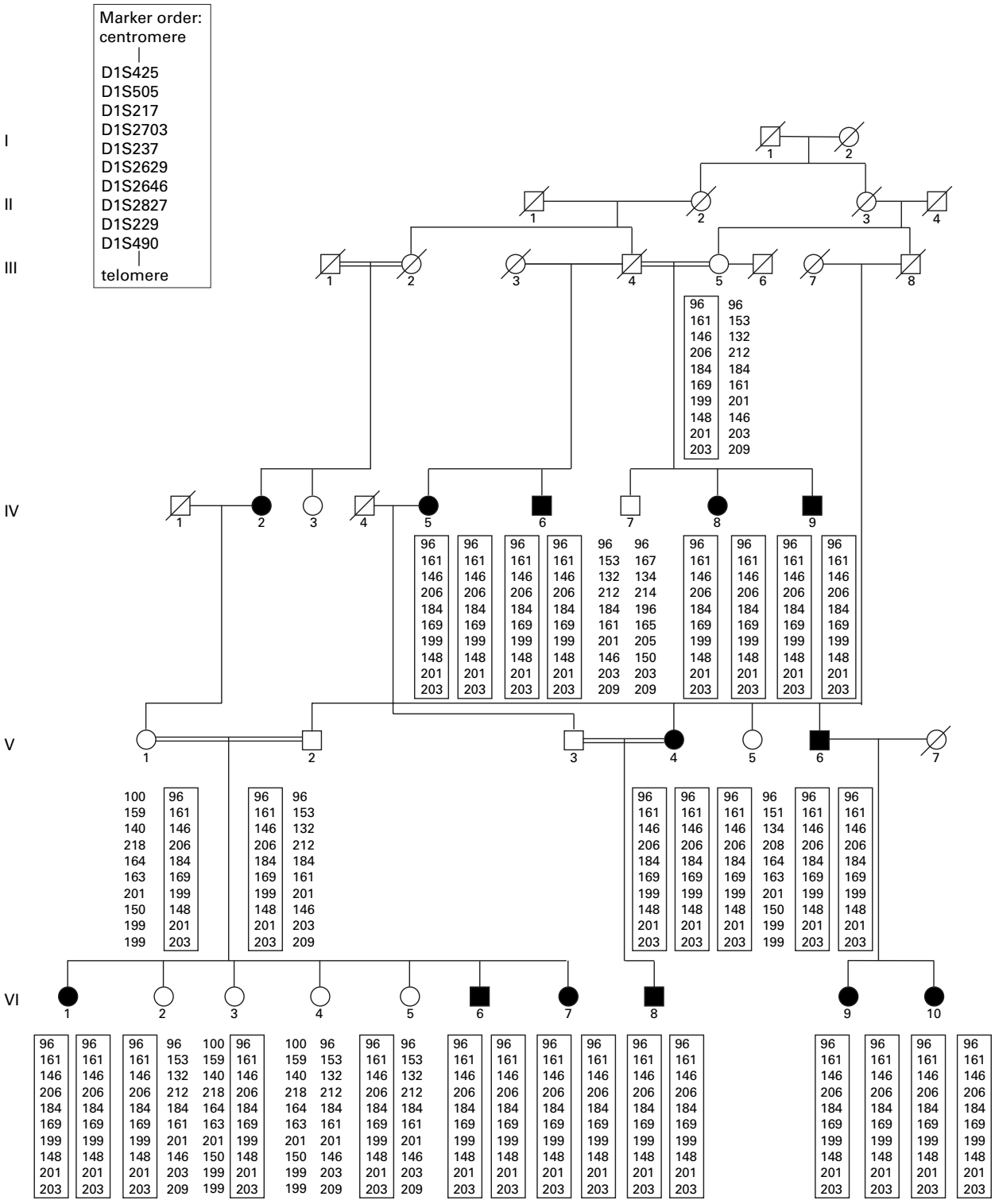

Figure 2 Pedigree of the Usher family from the Cayman Islands available for linkage analysis. The whole family contains several additional branches of complex relationships, but because of the limited capacity of the linkage programs these were not included in the linkage analysis. The subjects shown with haplotypes were included in the linkage analysis.

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