Letter to the Editor

Am. J. Hum. Genet. 78:357, 2006

USH1A: Chronicle of a Slow Death

To the Editor:

Usher syndrome type I (USH1) is an autosomal recessive condition characterized by profound congenital hearing impairment with unintelligible speech, early retinitis pigmentosa (usually within the 1st decade), and constant vestibular dysfunction (Fishman et al. 1983). USH1 is genetically heterogeneous, since seven different loci have been mapped to human chromosomes, five of which are identified: *USH1A* on 14q32.1 (MIM 276900), *USH1B* on 11q13.5 (myosin VIIA [MIM 276903]), *USH1C* on 11p15.1 (harmonin [MIM 276904]), *USH1D* on 10q21–q22 (cadherin 23 [MIM 601067]), *USH1E* on 21q21 (MIM 602097), *USH1F* on 10q21–22 (protocadherin 15 [MIM 602083]), and *USH1G* on 17q24–q25 (SANS [MIM 606943]).

The *USH1A* locus was described in 1992 in nine families originating from the same small area of the Poitou-Charentes region, around the town of Bressuire in France (Kaplan et al. 1992; Larget-Piet et al. 1994). The symbol "*USH1A*" and the additional trivial designation of "French variety" was assigned to that form of Usher syndrome.

In 1995, mutations of the unconventional myosin VIIA (GenBank accession number NM_000260) were found to account for the *USH1B* locus (Kimberling et al. 1992; Weil et al. 1995). Myosin VIIA is believed to play a role in the transport of membrane-associated proteins at apical surfaces of cells and, in the inner ear, it may be essential for adhesion between stereocilia (Keats and Savas 2004).

Candidate genes at the *USH1A* locus were selected with regard to these functional data. Four attractive candidate genes were studied in turn: (1) the gene encoding cyclin K (*CCNK,* also known as *CPR4* [GenBank accession numbers AF270825–AF270832]), whose expression in mouse overlaps with myosin VIIA (Edwards et al. 1997); (2) the gene encoding human echinoderm microtubule-associated protein-like (*HuEMAP* [GenBank accession number AJ420603]), a protein that may modify the dynamics of microtubules and that had long been regarded as a "strong candidate for the Usher syndrome type IA gene" (Eudy et al. 1997); (3) the gene encoding the Kinesin-light chain 2 (*KNS2* [GenBank accession numbers AF267517–AF267531]), which belongs to a class of microtubule-associated motor proteins (Cabeza-Arvelaiz et al. 1993); and, finally, (4) the gene encoding the human jagged 2 (*JAG2*) protein, a ligand which activates the Notch and related receptors and was suggested to play a role in the regulation of hair development in the inner ear (Oda et al. 1997; Lanford et al. 1999; Deng et al. 2000). As for *HuEMAP,* the *JAG2* gene had also long been regarded as a strong candidate for *USH1A*. All these genes were sequenced in one patient of each of the nine *USH1A* families originating from the Bressuire region, but no disease-associated alteration has been identified in any of them.

Later, we had the opportunity to study an additional multiplex family affected with Usher syndrome type I originating from the Bressuire region. Surprisingly, in this family, linkage of the disease gene to the *USH1A* locus was clearly excluded, but it was compatible with the *USH1B* locus.

Furthermore, we had the opportunity to study a last-born, healthy individual belonging to one of the eight original *USH1A* families of Bressuire reported in 1992 (individual II6, family 1) (Kaplan et al. 1992). Surprisingly, this healthy individual, who was unavailable in 1992, turned out to be haploidentical to his two affected sibs, which strongly challenges for the first time the existence of the *USH1A* locus.

At that time, these two unexpected data prompted us to screen for mutations in the major USH1 gene, the myosin VIIA in *USH1A* families. The results of this study signed the death warrant of the *USH1A* locus, since mutations were identified in six of these nine original families hailing from the Bressuire region (table 1).

In summary, among the 10 families originating from the Bressuire region (9 reported by Larget-Piet et al. [1994] and 1 additional family reported in this letter), 7 harbored mutations in the myosin VIIA gene, 1 was compatible with linkage to the *USH1D* and *USH1E* loci, and 1 excluded all USH1 loci (including the 14q32.1 region). With regard to the last family, no DNA was available for further linkage studies at all USH1 loci.

What lessons can one draw from this disappointing history? First of all, we should not have made the hypothesis of a founder effect without evidence for linkage

Table 1

Myosin VIIA Mutations Identified in Seven USH1 Families Originating from Bressuire

	Allele 1			Allele 2		
Family	Exon	Nucleotide Change	Predicted Change	Exon	Nucleotide Change	Predicted Change
2	48	c.6557T→C	p.Leu2186Pro[a]	43	c.5884-5887delTTCT	p.Phe1962fsX1968
4.II3	21	c.2513G→A	p.Trp838X	9	c.938delC	p.Thr313fsX361
4.II4	9	c.999T→G	p.Tyr333X	29	c.3719G→A	p.Arg1240Gln[b]
4.II5	29	c.3719G→A	p.Arg1240Gln[b]	9	c.999T→G	p.Tyr333X
4.III1	21	c.2513G→A	p.Trp838X	9	c.999T→G	p.Tyr333X
5	44	c.6025delG	p.Ala2009fsX2040	44	c.6025delG	p.Ala2009fsX2040
6	8	c.755A→G	p.Tyr252Cys[a]	37	c.5101C→T	p.Arg1701X
7	31	c.4012delC	p.Arg1338fsX1398	43	c.5884-5887delTTCT	p.Phe1962fsX1968
9	6	c.494C→T	p.Thr165M[c]	6	c.494C→T	p.Thr165M[c]
Novel Family	44	c.6025delG	p.Ala2009X2040	9	c.999T→G	p.Tyr333X

Note.—The A of the start codon (ATG) of the GenBank cDNA sequence is nucleotide +1 for the myosin VIIA gene. The numbers of families and of individuals of family 4, which consists of four nuclear subfamilies, refer to Larget-Piet et al. (1994).

[a] Original mutation absent from 100 control individuals (200 chromosomes).

[b] Janecke et al. 1999.

[c] Ouyang et al. 2005.

disequilibrium. Consequently, the Morton test used in the original study (Kaplan et al. 1992) may not always be applicable when the geographic origin is the only criterion for the subdivision of families. Second, we fell in love with the hypothesis of a "French variety" of USH1 because, in the middle of the 19th century, the first Institution for Deaf and Blind Children was created in the Poitou-Charentes region to receive 16 unrelated deaf and blind children. It is probable that some of them were affected with Usher syndrome. With consideration of the lack of intermixing of populations at this time, it is conceivable that one USH1 mutation settled in the region. Besides, after the mapping of the *USH1A* locus on chromosome 14q32.1, many very attractive candidate genes lying within the genetic interval were offered to our group for mutational screening in patients. To date, in light of our recent genetic studies showing that most patients of Bressuire harbor different myosin VIIA mutations, it is likely that, when the Institution for Deaf and Blind Children opened, several USH1 families moved to the Poitou-Charentes region and that several of these mutations were transmitted through generations. This was also the case in the Newfoundland population from an isolated region of Canada where a high incidence of Bardet-Biedl syndrome (BBS) exists. The genetic study of 17 BBS kindreds hailing from this region showed that at least four loci might account for the disease (Woods et al. 1999).

In conclusion, it is now clear that (1) the *USH1A* locus does not exist; (2) the myosin VIIA gene is the major USH1 gene, and, finally, (3) in our series, all USH1 loci were excluded in one *USH1A* family, suggesting that at least one additional gene should be identified.

Acknowledgments

We are very grateful to all families who agreed to send new blood samples. We thank Dominique Weil for providing us with the myosin VIIA primers. This work was supported by the Association Retina France.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/GenBank/ (for *CCNK* [accession numbers AF270825–AF270832], *HuEMAP* [accession number AJ420603], *KNS2* [accession numbers AF267517–AF267531], and myosin VIIA [accession number NM_000260])

Online Mendelian Inheritance in Man (OMIM), http:// www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM/ (for *USH1A, USH1B, USH1C, USH1D, USH1E, USH1F,* and *USH1G*)

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0002-9297/2006/7802-0018$15.00