

## **Practical guidelines for molecular testing in Usher syndrome**

**Disease definition :** Usher syndrome is an autosomal recessive combination of hearing loss with retinitis pigmentosa.

**Frequency :** Usher syndrome affects approximately 1 in 20.000 persons.

**Main clinical symptoms :** Usher syndrome is characterized by severe to profound, bilateral, sensorineural hearing loss, and progressive retinitis pigmentosa. The hearing loss in most cases is prelingual, and severe to profound. The retinitis pigmentosa results in night blindness, constricted visual fields progressing to tunnel vision, and impaired visual acuity progressing to total blindness. Additionally, vestibular areflexia is present in patients with Usher syndrome type 1.

**Inheritance :** Usher syndrome is always inherited in autosomal recessive way. Heterozygotes are asymptomatic, but may show abnormal electroretinography .

**Clinical diagnosis :** If Usher is suspected, an audiogram or BERA should be made to evaluate the hearing loss. Funduscopy, visual acuity and visual field determination, and electroretinography (ERG) should be performed to diagnose retinitis pigmentosa. Also in all children with severe prelingual hearing loss, RP should be excluded by ophthalmologic, electrophysiologic or molecular testing, as 5 % of the children with prelingual hearing loss turn out to have Usher syndrome .

**Clinical classification :** Usher syndrome can be subdivided in Usher syndrome types 1, 2 and 3:

- Usher syndrome type 1 is the most severe form characterised by congenital, severe to profound deafness, retinitis pigmentosa with pre-pubertal onset, and vestibular areflexia. The latter feature results in delayed motor development and reduced balance control.
- Usher syndrome type 2 is characterised by moderate (low frequencies) to severe (higher frequencies) congenital hearing loss, and later onset of retinitis pigmentosa, whereas vestibular areflexia is absent
- Usher syndrome type 3 is characterized by postlingual progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function. Certainly in the first decades there is

overlap with Usher syndrome type 2. Usher syndrome type III has been estimated to comprise 2% of all Usher syndrome cases.

**Molecular testing** : Up to now more than 10 loci with 8 nuclear genes MYO7A, CDH23, PCDH15, USH1C, USH1G, USH2A, GPR98, and USH3A have been shown to be implicated in Usher syndrome, with all 8 proteins being integrated into a single protein network, interacting with harmonin. Molecular testing in Usher syndrome is complicated by the large size of the disease genes: altogether the 8 genes comprise 347 protein-coding exons. The genes harbouring the majority of mutations MYO7A, CDH23, and USH2A are each at least 40 exons large, making testing very expensive. Furthermore, there are no real mutation hot spots, apart from  
However, a microarray-based test of more than 400 mutations in all 8 Usher disease genes MYO7A, CDH23, PCDH15, USH1C, USH1G, USH2A, GPR98, and USH3A is available. As this test detects 40-50 % of mutations in Usher type 1, 20-25 % of type 2, and 30 % of type 3, it is the first-pass screening tool.

- Usher syndrome type 1: Five genes have so far been shown to cause type 1: MYO7A (USH1B) encoding Myosin 7A, USH1C encoding Harmonin, CDH23 (USH1D) encoding Cadherin23, PCDH15 (USH1F) encoding Protocadherin15, and USH1G encoding Usher syndrome type-1G protein. A sixth locus USH1E has been mapped to chromosome, but the gene has not yet been isolated. MYO7A mutations represent 40-50% of all mutations in patients with Usher syndrome type 1, but is expensive as the gene is large.
- Usher syndrome type 2: 2 genes have so far been shown to cause type 2 : the USH2A gene encoding Usherlin, and the GPR98 (VLGR1B, USH2C) gene encoding the G-protein-coupled 7-transmembrane receptor GPR98. The USH2A gene accounts for 80% of patients with Usher syndrome type 2, with the 2299delG mutation being the most common mutation (> 50 %). Therefore, it is advisable to start testing type 2 patients with the 2299delG mutation in USH2A. The GPR98 gene harbours about 15% of mutations in Usher syndrome type 2. A third gene USH2B has been mapped to 3p24.2-p23, but not yet identified.
- Usher syndrome type 3: only 1 gene has been shown to cause type 3: the USH3A gene encodes clarin 1, a member of the clarin family. As this gene has only 4 exons, it is advisable to start testing type 3 patients with USH3A.

## References

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## Databases

HGMD database : [www.hgmd.cf.ac.uk](http://www.hgmd.cf.ac.uk)

Harvard Medical School Center for Hereditary deafness database :  
<http://hearing.harvard.edu/db/genelist.htm>

retina-international database: [www.retina-international.org](http://www.retina-international.org)

Table 1. Different types of Usher syndrome with the proportion of the respective gene, its size, and price.

Type	Gene	Protein	Gene contribution (%)	Number of exons (AA)	Price (Euro)
<b>Usher type 1</b>	MYO7A (USH1A, USH1B)	Myosin-VIIa	40-50	49 exons (2091 AA)	1600
	CDH23 (USH1D)	Cadherin-23	20-35	69 exons (3359 AA)	
	PCDH15 (USH1F)	Protocadherin-15	10-20	33 exons (1955 AA)	
	USH1C	Harmonin	6-7	28 exons (899 AA)	
	USH1G	SANS	7	3 exons (461 AA)	
<b>Usher type 2</b>	USH2A	Usherin	80	72 exons (5202 AA)	
	USH2A	Usherin	15	Exon 13 (2299delG mutation)	370
	GPR98 (USH2C)	G-protein coupled receptor 98	15	90 exons (6307 AA)	
<b>Usher type 3</b>	USH3A (USH3)	Clarin 1	?	4 exons (232 AA)	
<b>All cases</b>	MYO7A, CDH23, USH1C, USH1G, USH2A, MASS1, USH3A, PCDH15	Various	40-50 % of type 1 20-25 % of type 2 30 % of type 3	429 mutations	600

Figure 1. Suggested molecular testing in different types of Usher syndrome

### Usher syndrome

