The Genetics of Usher Syndrome in the Israeli and Palestinian Populations

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Supplementary Table 1: Mutations that were reported previously to cause USH and initially screened in our cohort.

Gene	c.	p.	Exon	Disease	Inheritance Pattern	Origin
USH2A	c.236_239dup	p.Gln81Tyrfs*28	2	USH2/ RP	AR	Oriental Jews ; Yemenite Jews
USH2A	c.1000C>T	p.R334W	6	USH2/ RP	AR	North African Jews
USH2A	c.2209C>T	p.R737*	13	USH2/ RP	AR	Oriental Jews
USH2A	c.4544C>T	p.T1515M	21	USH2	AR	North African Jews
USH2A	c.5519G>T	p.G1840V	27	USH2	AR	North African Jews
USH2A	c.5776+1G>A	IVS28+1G>A	28	USH2/ RP	AR	Oriental Jews ; Yemenite Jews
USH2A	c.12067-2A>G	IVS61-2A>G	62	USH2	AR	Oriental Jews ; Yemenite Jews
USH3A	c.144T>G	p.N48K	1	USH3	AR	Ashkenazi Jews
MYO7A	c.641G>A	p.G214R	7	USH1	AR	North African Jews
MYO7A	c.700C>T	p.Q234*	7	USH1	AR	Arab Muslims
MYO7A	c.2065delC	p.L689Cfs*4	45	USH1	AR	North African Jews
MYO7A	c.2476G>A	p.A826T	21	USH1	AR	North African Jews
MYO7A	c.5581C>T	p.R1861*	40	USH1	AR	Samaria Jews

Supplementary Table 2: Summary of whole exome sequencing analysis

Pt. #	Consanguinity	Total no. of variants	No. of missense, nonsense, insertions and deletions within the ORF, and splicing variants	No. of variants in ExAc (MAF>0.05)	No. of Homozygous variants	No. of variants within linked regions after filtering	No. of variants in USH Genes after filtering
MOL0078-1	None	85234	10736	3412	302	NA	2 (USH2A)
MOL0104-1	2:2	96485	10836	2147	203	26	1 (MYO7A)
MOL0244-3	None	78857	12415	2106	NA	NA	2 (USH2A)
MOL0406-2	3:3	103894	10916	2105	230	NA	1 (MYO7A)
MOL0512-1	3:3	108485	10784	1868	212	1	1 (GPR98)
MOL0514-1	None	121641	11408	2310	NA	NA	2 (MYO7A)
MOL0823-1	None	101435	10564	3412	256	NA	1 (MYO7A)
MOL0853-1	2:2	155399	11512	2451	218	NA	1 (USH2A)
MOL0962-1	None	67317	13963	4946	903	1	1 (MYO7A)
MOL1087-4	Distantly related	78452	11766	3944	45	NA	1 (USH2A)
MOL1542-1	2:2	46088	10010	1503	160	NA	1 (MYO7A)

Supplementary Table 3: Clinical data of patients with mutations in USH-causing genes

Pt. # (age-years) *	Genotype	Best Corrected Visual Acuity (age)*	Refraction (age)*	Full Field ERG Results			EOG (%)	Hearing loss
				Cone Flicker - 30Hz (IT msec)	Mixed Cone-Rod Response (μ V)	Rod Response - Blue Light (b, μ V)		
104-1 (1)	MYO7A c.5069_5070insC p.Q1690fs homo	0.15 (17)	NA	Extinguish	Extinguish	Extinguish	NA	NA
104-2 (20)	MYO7A c.5069_5070insC p.Q1690fs homo	0.3 (23)	Sph (6)	Trace response	Trace response	Trace response	100	NA
106-3 (18)	USH2A- IVS61-2A>G homo	0.73	-7.5	Trace response	Extinguished	Extinguished	NA	NA
244-3 (37)	USH2A- comp het for T80fs and IVS28+1G>A	0.1258 (48)	-2.0	Extinguished	Extinguished	Extinguished	100	NA
244-1 (34)	USH2A- comp het for T80fs and IVS28+1G>A	NA	-1.75	Extinguished	Extinguished	Extinguished	112	NA
406-1 (17)	MYO7A- c.G3892A, p.G1298R homo	1.0	+1.5 (10)	Extinguished	Extinguished	Extinguished	NA	NA
512-1 (18)	GPR98- c.15494delA, p.K5165fs homo	0.33	NA	Extinguished	Extinguished	Extinguished	NA	NA
512-2 (6)	GPR98- c.15494delA, p.K5165fs homo	0.67	-5.5	35	NA	NA	NA	NA
594-1 (11)	USH2A- c.802G>A, p.G268R homo	0.6 (11) 0.4 (17)	-3.75 (17)	Extinguished	Extinguished	Extinguished	NA	Since age 5
594-3 (10)	USH2A- c.802G>A, p.G268R homo	1.0	NA	37 (38.5)	a-56 b-127	Extinguished	NA	Hearing aid BE
594-5 (7)	USH2A- c.802G>A, p.G268R hetero	0.5	NA	Trace response	a- 27 b- 64	Extinguished	NA	No hearing problems

Pt. # (age-years) *	Genotype	Best Corrected Visual Acuity (age)*	Refraction (age)*	Full Field ERG Results			EOG (%)	Hearing loss
				Cone Flicker - 30Hz (IT msec)	Mixed Cone-Rod Response (μ V)	Rod Response - Blue Light (b, μ V)		
675-1 (23)	CLRN1: c.144T>G, p.N48K homo	0.56	-1.25	Trace response	Extinguished	Extinguished	NA	NA
770-1	MYO7A- c.5581C>T p.R1861* homo	0.4	-1.50	NA	NA	NA	NA	NA
853-1 (23)	USH2A c.14424C>A p.C4808* homo	0.8 (27)	-4.5 (27)	Extinguished	Extinguished	Extinguished	NA	NA
853-2 (30)	USH2A c.14424C>A p.C4808* homo	NA	NA	16	Extinguished	Extinguished	NA	NA
853-3 (21)	USH2A c.14424C>A p.C4808* homo	0.85	-3.0	Extinguished	Extinguished	Extinguished	NA	NA
867-1 (12)	USH2A- IVS61-2A>G homo	0.45	-5.0	32	a- 93 b- 105	0	NA	NA
867-2 (21)	USH2A- IVS61-2A>G homo	0.67	-7.5	Trace response	Extinguished	Extinguished	NA	NA
920-1 (12)	MYO7A- c.700C>T, p.Q234*	NA	NA	Trace response	Trace response	Extinguished	NA	Cochlear Implant (RE)
973-1 (42)	USH2A- IVS61-2A>G homo	0.45	NA	Extinguished	Extinguished	Extinguished	NA	NA
1019-1 (5)	MYO7A- IVS18+1G>T homo	NA	-0.5	Extinguished	NA	NA	NA	NA
1021-1 (10)	CLRN1- N48K het and p.Tyr176* het	0.9	NA	Trace response	Extinguished	Extinguished	100	NA
1087-1 (34)	USH2A- p.G268R homo	0.17	-2.0	15	Extinguished	Extinguished	100	NA
1087-5 (34)	USH2A- p.G268R homo	0.25	-5.5	12	Extinguished	Extinguished	NA	NA

Pt. # (age-years) *	Genotype	Best Corrected Visual Acuity (age)*	Refraction (age)*	Full Field ERG Results			EOG (%)	Hearing loss
				Cone Flicker - 30Hz (IT msec)	Mixed Cone-Rod Response (μ V)	Rod Response - Blue Light (b, μ V)		
1191-1 (4)	MYO7A-IVS18+1G>T homo	0.73	-7.5	Extinguished	Extinguished	NA	NA	NA
1191-2 (0.5)	MYO7A-IVS18+1G>T homo	NA	NA	29	Extinguished	NA	NA	NA

NA- not available.

Supplementary Table 4: Homozygosity mapping results of families in which disease-causing mutations were identified

Family no.	Phenotype	Subject/s no.	Chromosome	Homozygous region
MOL0104	USH1	104-1,2	1 3 6	109-166 (57Mb) 30-58 (28Mb) 133-156 (23Mb)
MOL0512	USH1	512-1,2	13 5	78-96 (18Mb) 83-95 (12Mb)
MOL0514	USH1	514-1	3 19	78.6-94.3 (16Mb) 31-51.5 (20Mb)
MOL0569	USH1	569-1	11	61-92 (29Mb)
MOL0594	USH2	594-1,2	1	173-195 (23Mb), 202-230 (28Mb)
MOL0620	USH2	620-2	1	211.5-237.5 (26Mb)
MOL0962	USH1	962-1	11	75.3-83.1 (8Mb)
MOL0973	USH2	973-2,4	1 4 5 8 21	212-215.8 (3.8Mb) 189.1-191.2 (>2.1Mb) 158.9-163.5 (4.6Mb) 103.9-109.7 (5.8Mb) 42.6-46.9 (>4.3Mb)

Supplementary Table 5: A list of missense mutations with different pathogenicity prediction tools and frequency in exome databases

Gene	Mutation Name	MAF at ExAC	EVS	Prediction tools	
				Mutation Taster (Probability)	**Polyphen-2 (Score)**
MYO7A	c.640G>A p.G214R	0	0	Disease causing (1)	Probably damaging (1.00)
MYO7A	c.2476G>A p.A826T	0.003924	0	Disease causing (0.99)	Possibly damaging (0.600)
MYO7A	c.3892G>A p.G1298R	0	0	Disease causing (1)	Probably damaging (1.00)
USH2A	c.802G>A p.G268R	0.00001	0	Disease causing (1)	Probably damaging (1.00)
USH2A	c.1000C>T p.R334W	0.00004125	0	Disease causing (1)	Probably damaging (1.00)
USH2A	c.5519G>T p.G1840V	0	0	Disease causing (1)	Probably damaging (1.00)
CLRN1	c.144T>G p.N48K	0.00021	0	Disease causing (1)	Probably damaging (1.00)

MAF at ExAC- minor allele frequency at Exome Aggregation Consortium (http://exac.broadinstitute.org/); **EVS**- Exome Variant Server (http://evs.gs.washington.edu/EVS/); **Polyphen2**- http://genetics.bwh.harvard.edu/pph2/; **MutationTaster**- http://www.mutationtaster.org/

Supplementary Table 6: Usher syndrome families together with the mutation detection methods, screened mutations and the pending analysis for the unsolved families. Solved families are marked in yellow. Screened founder mutations are detailed in the third column indicated as Ex which refer to exon followed by the exon number. WES- Whole exome sequencing, ar- Autosomal recessive, i- isolate case.

Family #	Inheritance pattern and diagnosis	Sanger mutation screen	Homozygosity mapping	WES	Identified Mutation/s	Reported by us Previously
MOL0028	arUSH (atypical)	Done	Done	Done	CEP250- c.3463C>T homo	[1]
MOL0035	arUSH2	Done			USH2A- c.236_239dup homo	[2 3]
MOL0043	arUSH1	Done				
MOL0051	arUSH2	Done			USH2A- compound heterozygous: c.236_239dup and c.2209C>T	[2]
MOL0078	arUSH2	Done		Done	USH2A- compound heterozygous: c.5776+1G>A and c.7595-2144A>G	
MOL0094	arUSH2	Done		Done	USH2A- c.1000C>T homozygous	[3]
MOL0104	arUSH1		Done	Done	MYO7A- c.5069_5070insC homozygous	
MOL0106	arUSH2	Done			USH2A- c.12067-2A>G homozygous	
MOL0109	arUSH2	Done			USH2A- c.236_239dup homozygous	
MOL0120	arUSH (atypical)	Done	Done	Done	ARSG- c.133G>T homozygous	[4]

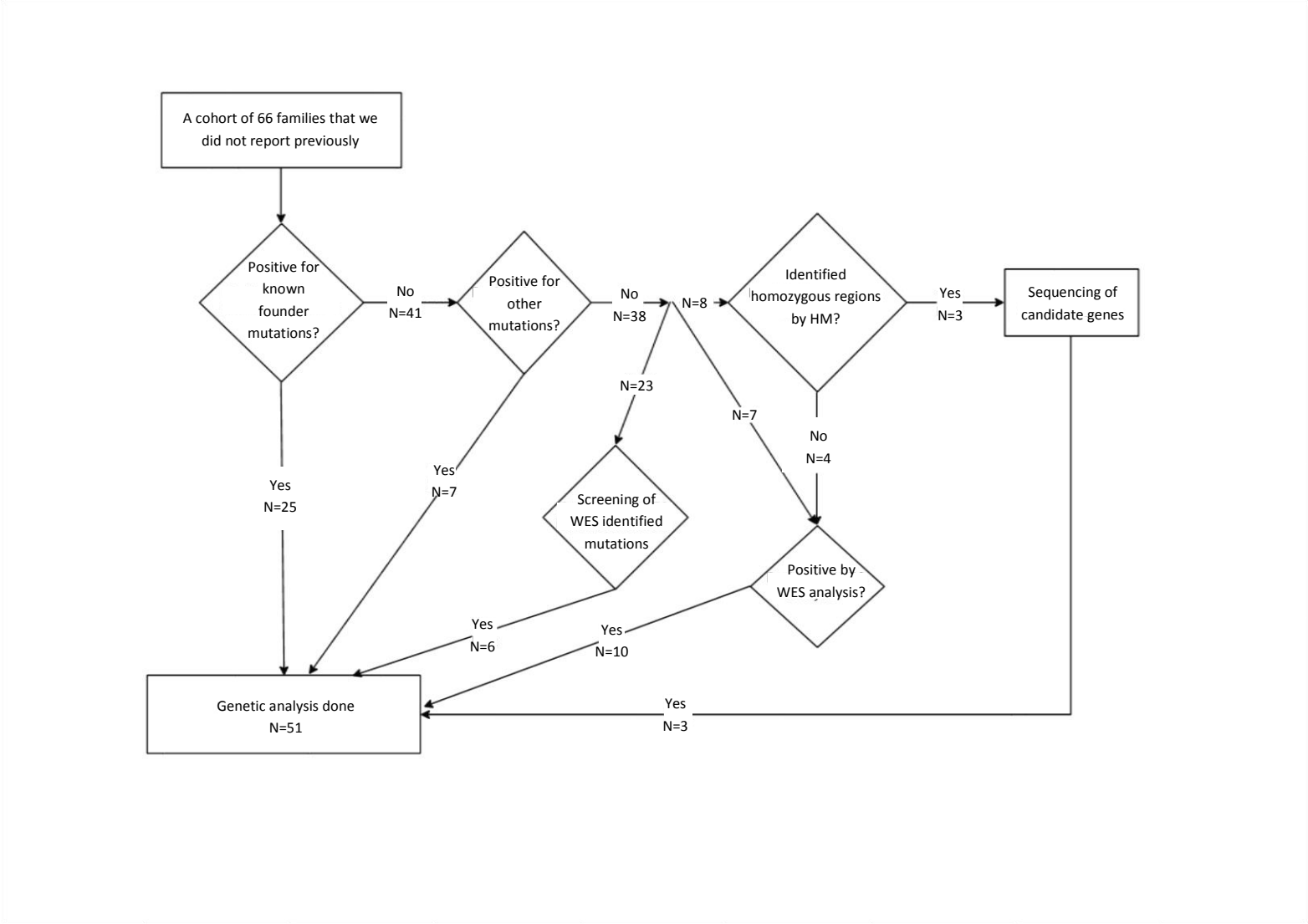
MOL0149	arUSH2	Done			USH2A- c.12067-2A>G homozygous	[3]
MOL0165	arUSH2	Done			USH2A- c.2209C>T homozygous	[2]
MOL0243	arUSH3	Done			CLRN1- c.144T>G homozygous	
MOL0244	arUSH2			Done	USH2A- compound heterozygous: c.236_239dup and c.5776+1G>A	
MOL0280	arUSH2	Done			USH2A- c.1000C>T homozygous	
MOL0320	arUSH1	Done			MYO7A- c.700C>T homozygous	
MOL0324	arUSH2	Done			USH2A- compound heterozygous: c.236_239dup and c.12067-2A>G	
MOL0334	iUSH2/3	Done				
MOL0356	arUSH3	Done			CLRN1- c.144T>G homozygous	
MOL0365	arUSH2	Done			USH2A- c.14023A>T homozygous	
MOL0366	arUSH2	Done			USH2A- c.8558+1G>T homozygous	
MOL0370	arUSH3	Done			CLRN1- c.144T>G homozygous	
MOL0384	arUSH2	Done			USH2A- c.5519G>T homozygous	
MOL0406	arUSH1			Done	MYO7A- c.3892G>A homozygous	
MOL0467	arUSH1	Done		Done	MYO7A- c.6355-16_6811del homozygous	[5]
MOL0512	arUSH2		Done	Done	*GPR98*- c.15494delA homozygous	
MOL0514	arUSH1		Done	Done	MYO7A- compound heterozygous: c.3892G>A and c.2187+1G>T	

MOL0569	arUSH1	Done	Done		MYO7A- c.285+2T>G homozygous	
MOL0594	arUSH2	Done			USH2A- c.802G>A homozygous	
MOL0620	arUSH2	Done	Done		USH2A- c.236_239dup homozygous	
MOL0675	arUSH3	Done			CLRN1- c.144T>G homozygous	
MOL0691	arUSH1/2	Done				
MOL0722	iUSH2	Done				
MOL0737	arUSH (atypical)			Done	ARSG- c.133G>T homozygous	[4]
MOL0770	arUSH1	Done			MYO7A- c.5581C>T homozygous	
MOL0780	iUSH2	Done				
MOL0823	iUSH1	Done		Done	MYO7A- c.551G>A heterozygous	
MOL0837	arUSH2	Done			USH2A- c.236_239dup homozygous	
MOL0841	arUSH1	Done			MYO7A- c.5101C>T homozygous	
MOL0847	iUSH2/3	Done				
MOL0853	arUSH2			Done	USH2A- c.14424C>A homozygous	
MOL0861	arUSH2	Done				
MOL0867	arUSH2	Done			USH2A- c.12067-2A>G homozygous	
MOL0881	arUSH1	Done			MYO7A- compound heterozygous: c.285+2T>G and c.2476G>A	

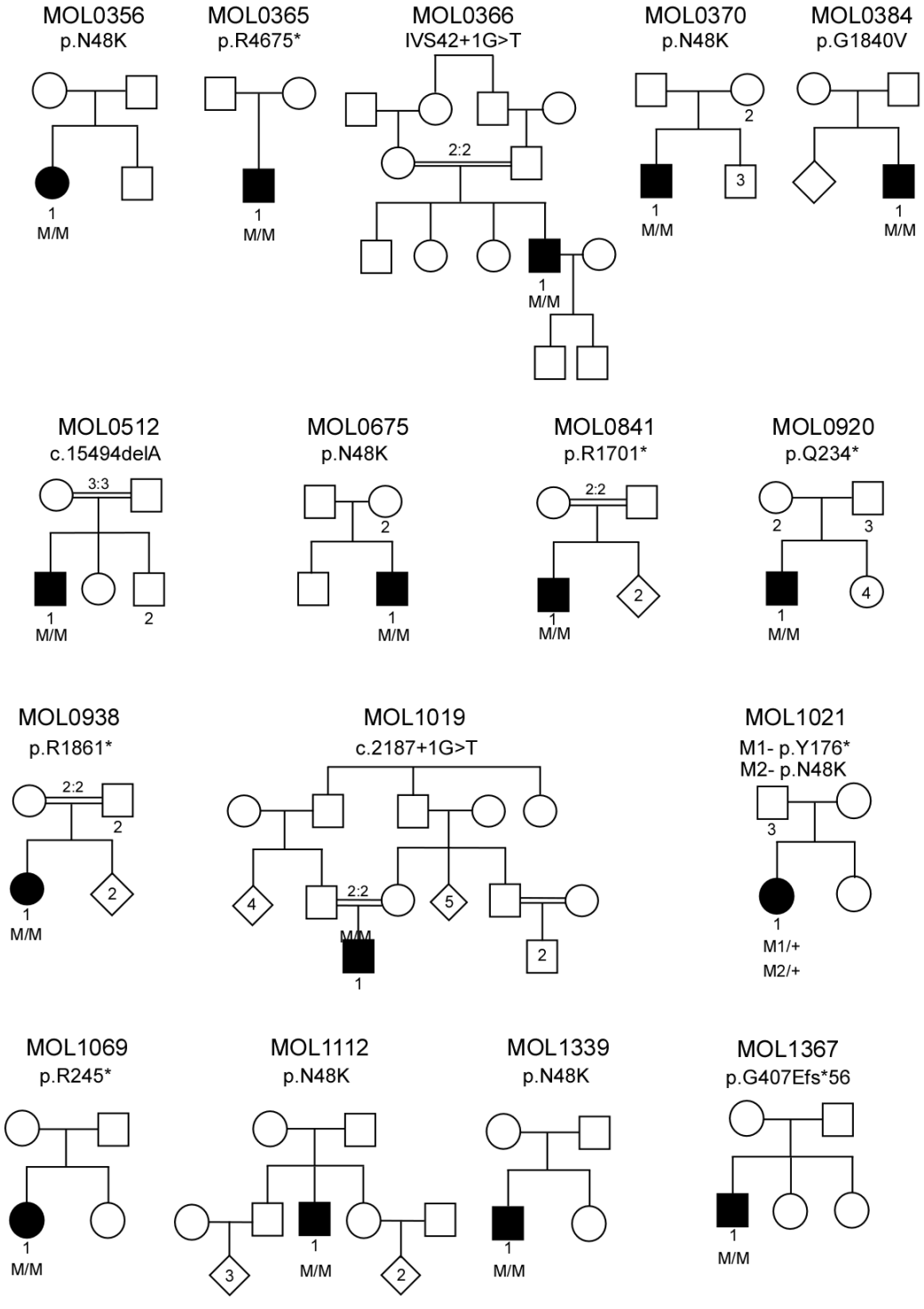
MOL0889	iUSH2	Done				
MOL0917	iUSH2	Done				
MOL0920	arUSH1	Done			MYO7A- c.700C>T homozygous	
MOL0933	I(ar)USH2	Done				
MOL0938	arUSH1	Done			MYO7A- c.5581C>T homozygous	
MOL0941	iUSH2/3	Done				
MOL0944	iUSH2	Done				
MOL0962	arUSH1		Done	Done	MYO7A- c.2307delC homozygous	
MOL0973	arUSH2	Done	Done		USH2A- c.12067-2A>G homozygous	
MOL0997	arUSH1	Done				
MOL1019	arUSH1	Done			MYO7A- c.2187+1G>T homozygous	
MOL1021	arUSH3	Done			CLRN1- compound heterozygous: c.144T>G and c.528T>G	
MOL1069	arUSH1	Done			PCDH15- c.733C>T homozygous	
MOL1087	arUSH2			Done	USH2A- c.802G>A homozygous	
MOL1111	iUSH2	**Done**			USH2A- c.12067-2A>G heterozygous (all exons screened)	
MOL1112	arUSH3	Done			CLRN1- c.144T>G homozygous	
MOL1178	iUSH1	Done				

MOL1191	arUSH1	Done			MYO7A- c.2187+1G>T homozygous	
MOL1207	iUSH2	Done				
MOL1308	iUSH1	Done			PCDH15- c.733C>T heterozygous	
MOL1339	arUSH3	Done			CLRN1- c.144T>G homozygous	
MOL1345	iUSH2/3	Done				
MOL1359	iUSH2/3	Done				
MOL1367	arUSH	Done			USH1C- c.1220del homozygous	
MOL1382	iUSH	Done				
MOL1425	iUSH	Done				
MOL1430	arUSH1	Done			MYO7A- c.700C>T homozygous	
MOL1449	iUSH2	Done				
MOL1483	arUSH1	Done			MYO7A- c.700C>T homozygous	
MOL1542	arUSH1	Done		Done	MYO7A- c.6196C>T homozygous	

Supplementary Figure 1: A flow chart of the genetic analysis towards the identification of disease-causing mutations in 40 out of the 79 recruited families.



Supplementary Figure 2: Isolate case with USH and identified disease-causing mutations. Black symbols-patients with USH. Numbers under symbols indicate recruited individuals and numbers within diamonds/circles/ squares indicate the number of siblings. The genotype of recruited individuals is depicted below the individual number. The index case is indicated as individual #1.



SUPPLEMENTARY REFERENCES

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