Human non syndromic and syndromic hearing loss with vestibular dysfunction

Human related SNHL (OMIM)	Gene symbol	Location	Ear pathology/ gene function	Vestibular findings in human	Vestibular findings in animal models	References
NON SYNDROMIC HEARING LOSS						
DFNA1 (602121)	*DIAPH1*	5q31.3	Hair bundle development and functioning	Vestibular dysfunction not fully penetrant. Findings consistent with endolymphatic hydrops.		[1]
DFNA3 (121011-604418)	*GJB2 – GJB6*	13q12.11	Cochlea ion homeostasis	Vestibular dysfunction not fully penetrant. Otolithic and canalar dysfunction.	Reduced inner ear size, abnormal distribution of otoliths and reduced otolith size and developmentally delayed semicircular canals in cx30.3 zebrafish.	[2-4]
DFNA6/14 (606201)	*WFS1*	4p16.1	Oxidative stress, metabolims & mitochondria	Vestibular dysfunction in few patients.	Vestibular dysfunction in the mouse model (*tilted – tlt*): complete lack of otoconia in utricule and saccule.	[5, 6]
DFNA7 (600298)	*LMX1A*	1q23.3	Hair cell's adhesion and maintenance	About half of the affected individuals display vestibular dysfunction.	Vestibular dysfunction in the mouse model (*Lmx1a*): circling behavior, impaired righting reflex, hyperactivity.	[7-9]
DFNA9 (603196)	*COCH*	14q12	Transmembrane or secreted proteins and extracellular matrix	Variable vestibular dysfunction up to severe vestibular deficit/areflexia.	Vestibular dysfunction in the mouse model: abnormal vestibular evoked potentials	[10-18]
DFNA11 (276903)	*MYO7A*	11q13.5	Hair bundle development and functioning	Vestibular dysfunction not fully penetrant. Variable degree of vestibular dysfunction.		[19-21]
DFNA13 (120290)	*COL11A2*	6p21.32	Transmembrane or secreted proteins and extracellular matrix	Various caloric abnormalities observed in about half of the subject		[22]
DFNA15 (602460)	*POU4F3*	5q32	Hair cell's adhesion and maintenance	Vestibular dysfunction not fully penetrant. Mild to severe vestibular dysfunction.	*Pou4f3*$^{ddl/ddl}$ mice exhibit vertical head tossing, circling and general hyperactive behavior indicative of a vestibular dysfunction	[23-25]
DFNA17 (160775)	*MYH9*	22q12.3	Hair cell's adhesion and maintenance	Associated to cochleosaccular degeneration.		[26]
DFNA20/26 (102560)	*ACTG1*	17q25.3	Hair bundle development and functioning	Vestibular dysfunction not fully penetrant.		[27]

					Mild to severe hyporeflexia.	
DFNA22 (600970)	*MYO6*	6q14.1	Hair bundle development and functioning		Vestibular dysfunction in mouse with MYO6 mutation : the *Snell's waltzer* (sv) mouse and *Turner* (Tur) mouse.	[28, 29]
DFNA28 (608576)	*GRHL2*	8q22.3	Transcriptional regulation		Vestibular malformation and severe vestibular dysfunction in zebrafish model.	[30]
DFNA41 (600844)	*P2RX2*	12q24.33	Cochlea ion homeostasis		Vestibular dysfunction observed in knock-in mouse model of DFNA41: impaired balance on rotarod and beam walking.	[31]
DFNA69 (184745)	*KITLG*	12q21.32	Transmembrane or secreted proteins and extracellular matrix	Vestibular dysfunction not fully penetrant.		[32]
DFNA76 (602734)	*PLS1*	3q23	Hair bundle development and functioning		Thresholds for vestibular evoked potentials are significantly elevated in mice lacking functional PLS1.	[33]
DFNA78 (610981)	*SLC12A2*	5q23.3	Cochlea ion homeostasis	Vestibular dysfunction with delayed motor skills.	Severe vestibular dysfunction observed in *Slc12a2*$^{-/-}$ mice: head bobbing, circling, collapse of vestibular compartments and epithelia.	[34-36]
DFNB1 (121011 – 604418)	*GJB2* -GJB6 (Cx26 - Cx30)	13q12.11	Cochlea ion homeostasis	Vertigo reported by approximately half of the affected subjects.	Reduced inner ear size, abnormal distribution of otoliths and reduced otolith size and developmentally delayed semicircular canals in cx30.3 zebrafish.	[4, 37]
DFNB2 (276903)	*MYO7A*	11q13.5	Hair bundle development and functioning	Vestibular dysfunction not fully penetrant.		[38]
DFNB3 (602666)	*MYO15A*	17p11.2	Hair bundle development and functioning		Vestibular dysfunction in mouse model of DFNB3 *shaker-2*: head-tossing, circling behavior	[39, 40]
DFNB4 (605646)	*SLC26A4*	7q22.3	Cochlea ion homeostasis	Enlarge vestibular aqueduct and possible Mondini dysplasia. Vestibular dysfunction not fully penetrant.		[41]

DFNB6 (607237)	*TMIE*	3p21.31	Hair bundle development and functioning		Vestibular dysfunction in mouse model of DFNB6 *spinner*: head-shaking, circling behavior.	[42]
DFNB8/10 (605511)	*TMPRSS3*	21q22.3	Cochlea ion homeostasis	Vestibular dysfunction not fully penetrant. Mild vestibular dysfunction.	*Tmprss3*^{Y260X} mice display mild vestibular syndrome that correlated histologically with a slow degeneration of saccular hair cells.	[43, 44]
DFNB16 (606440)	*STRC*	15q15.3	Hair bundle development and functioning	Episodic vertigo. Primarly saccular and utricular dysfunction.		[45]
DFNB18B (604487)	OTOG	11p15.1	Transmembrane or secreted proteins and extracellular matrix	Vestibular dysfunction not fully penetrant. Some individuals have delayed age of walking.	Severe vestibular dysfunction in mouse model with Otog mutation (*Twister*).	[46-48]
DFNB23 (605514)	*PCDH15*	10q21.1	Hair bundle development and functioning		Vestibular dysfunction in animal model of recessive mutations of PCGH15 (*Ames Waltzer* (*av*) mouse)	[49]
DFNB25 (613283)	*GRXCR1*	4p13	Hair bundle development and functioning	Vestibular dysfunction not fully penetrant.		[50]
DFNB31 (607928)	*WRHN*	9q32	Hair bundle development and functioning		Vestibular dysfunction in mouse model of DFNB31 *Whirler (wi)*: circling and head-bobbing.	[51]
DFNB36 (606351)	*ESPN*	1p36.31	Hair bundle development and functioning	Vestibular areflexia.		[52]
DFNB37 (600970)	*MYO6*	6q14.1	Hair bundle development and functioning	Vestibular dysfunction in many individuals with delayed age of walking.		[53]
DFNB59 (610219)	*PJVK*	2q31.2	Oxidative stress, metabolims & mitochondria	Central vestibular dysfunction.		[54]
DFNB68 (605111)	*S1PR2*	19p13.2	Cochlea ion homeostasis		Vestibular dysfunction observed in *S1pr2*$^{-/-}$ mouse: head tilting, poor swimming ability, progressive deterioration of vestibular epithelium and loss or deformity of utricular and saccular otoconia. Vestibular dysfunction in zebrafish model: Structural	[55-59]

					defects are identified within the otic vesicle, the semicircular canals, otoliths, utricle, and saccule.	
DFNB82 (609245)	*GPSM2*	1p13.3	Hair bundle development and functioning		Vestibular dysfunction in mouse model with GPSM2 mutation: hyperactive behavior, circling, short stereocilia.	[60]
DFNB84 (603317)	*PTPRQ*	12q21.31	Hair bundle development and functioning	Severe vestibular dysfunction in all individuals.	Hair bundle defects are observed in the vestibule of *Ptprq*$^{-/-}$ mice. Vestibular dysfunction observed in Doberman Pinschers with PTPRQ mutation: head tilt.	[61-63]
DFNB101 (615762)	*GRXCR2*	5q32	Hair bundle development and functioning		Mouse *Grxcr2* deletion mutants exhibit abnormal vestibular evoked potentials.	[64]
DFNB103 (607293)	*CLIC5*	6p21.1	Hair bundle development and functioning Cochlea ion homeostasis	Vestibular dysfunction later in life.	Vestibular dysfunction in mouse model of DFNB103 *Jitterbug (jbg/jbg).*	[65, 66]
DFNB108 (602336)	ROR1	1p31.3	Synaptic transmission	Fusion of the cochlea and vestibule into a common cavity.		[67]
DFNB109 (612959)	*ESRP1*	1p13.3	Hair cell's adhesion and maintenance	Vestibular dysplasia.	Mouse Esrp1$^{-/-}$: common crus and lateral semicircular canal dysgenesis.	[68]
DFNB110 (603196)	*COCH*	14q12	Transmembrane or secreted proteins and extracellular matrix	Two individuals tested in their first decade of life: one with mild vestibular impairment, the other normal vestibular function.		[69]
DFNB111 (604873)	*MPZL2*	11q23.3	Hair cell's adhesion and maintenance	Slight modifications of the vestibular function.		[70]
DFNX2 (300039)	*POU3F4*	Xq21.1	Transcriptional regulation	Middle and inner ear malformation with perilymphatic Gusher. Severe vestibular dysfunction.	*Pou3f4*-deficient mice: impaired balance, loss of vestibular hair cells	[71, 72]
SYNDROMIC HEARING LOSS						
Jervell and Lange-Nielsen syndrome 1	*KCNQ1*		Cochlea ion homeostasis	Severe vestibular dysfunction and delayed motor skills.	Vestibular dysfunction in *Kcnq1*$^{-/-}$ mice: head-bobbing, circling, trouble righting themselves collapse of endolymphatic space.	[73, 74]
Jervell and Lange-Nielsen syndrome 2	*KCNE1*		Cochlea ion homeostasis	Severe vestibular dysfunction and delayed motor skills.	Vestibular dysfunction in *Kcne1*$^{-/-}$ mice: head-	[74, 75]

				bobbing, circling, abnormal development of the endolymphatic space, severe degeneration of the hair cells	
Waardenburg Type 1	*PAX3*	Melanocyte development	Vestibular dysfunction can be observed.		[76]
Waardenburg Type 2	*MITF SNAI2 SOX10*	Melanocyte development Melanocyte deficiency	Vestibular dysfunction can be observed. Dysmorphic vestibular anatomy linked to SOX10 mutation: bilateral agenesis or hypoplasia of the semicircular canals or both, associated with an enlarged vestibule and a cochlear deformity.		[76, 77]
Waardenburg Type 3	*PAX3*	Melanocyte development			[76]
Waardenburg Type4	*EDNRB EDN3 SOX10*	Melanocyte development	Severe vestibular dysfunction are observed. Dysmorphic vestibular anatomy linked to SOX10 mutation: bilateral agenesis or hypoplasia of the semicircular canals or both, associated with an enlarged vestibule and a cochlear deformity.		[76, 77]
USHER1B	*MYO7a*	Hair bundle development and functioning	Severe vestibular dysfunction with delayed motor skills.	Mouse model (*Shaker*): head-tossing, hyperactivity and circling behaviors. Disorganized stereociliary bundles. Zebrafish model (*mariner mutant*): circling swimming behavior. Disorganized stereociliary bundles.	[81-84]
USHER1D	*CDH23*	Hair bundle development and functioning	Severe vestibular dysfunction in most individuals with delayed motor skills. Missense mutations result in either a milder form, which overlaps with clinical types USH2 or 3, or nonsyndromic deafness (DFNB12)	Severe vestibular dysfunction in mouse model of USH1D *Waltzer*: hyperactivity, head-tossing, circling behavior. Severe vestibular dysfunction in zebrafish model: balance defect, circling swimming behavior.	[84-88]
USHER1F	*PCDH15*	Hair bundle development and functioning	Severe vestibular dysfunction with delayed motor skills.	Vestibular dysfunction described for mouse with	[49, 84, 89, 90]

				mutation of Pcdh15 *Ames waltzer (*av*)* and distorded stereocilia bundles. Vestibular defect in zebrafish Pcdh15 mutants.	
USHER1C	*Ush1c*	Hair bundle development and functioning Synaptic transmission	Severe vestibular dysfunction with delayed motor skills.	Severe vestibular dysfunction in mouse model of USH1C *Waltzer*: hyperactivity, head-tossing, circling behavior and disorganized stereocilia bundles. Severe vestibular dysfunction in zebrafish model of USH1C: circling swimming behavior, disorganized stereocilia bundles.	[84, 91-93]
USHER1G	*sans*	Hair bundle development and functioning	Severe vestibular dysfunction with delayed motor skills. Atypical USH1 has also been associated with mutations in the *SANS* gene (USH1G).		[84]
USHER Type 2	ADGRV1 VLGR1 GPR98 *USH2A* *WHRN*	Hair bundle development and functioning	Variable vestibular function.	*Whrn*^{wi} mice and *Whrn*^{neo} mice have severe to profound loss of linear vestibular evoked potential responses and shorter stereocilia.	[94, 95]
USHER Type 3	*CLRN1* *HARS*	Hair bundle development and functioning	Variable vestibular function.	Progressive vestibular loss in Clrn1-/- mice.	[96, 97]
Pendred	*SLC26A4* *EPHA2* *EPHB2*		Dysmorphic vestibular anatomy/ large vestibular aqueduct. Mild vestibular dysfunction primarly in saccul.	Mouse model *Slc26a4*$^{\Delta/\Delta}$ has an enlarged vestibular aqueduct and a Mondini-like dysplasia of the cochlea. Mouse model Ephb2: abnormal otoconia, dysplasia of endolymphatic fluid space, absence of endolymphatic duct.	[98-101]
DRTA	ATP6V1B1 ATP6V0A4	Absent endocochlear potential	Large vestibular aqueduct. Vestibular dysfunction can be observed.		[102]

BOR	*EYA1* *SIX1* *SIX5*	Inner ear development	Dysmorphic vestibular anatomy/ large vestibular aqueduct.	Mouse model: head bobbing, vestibular dysmorphy. Reduced number of hair cells. Zebrafish model: imbalanced and circling swimming behavior, small otoliths, absent hair cells in cristae, reduced number of hair cells in maculae	[103-108]
22q11 deletion syndrome			Frequent vestibular dysfunction. Frequent inner ear malformations particularly the lateral semi-circular canal .		[109, 110]
CHARGE	*Chd7* *Sema3e*	Inner ear development	Severe vestibular dysfunction with frequent delayed motor skills. Semi-circular canal hypoplasia or agenesis. Vestibulocochlear nerve hypoplasia.	Severe vestibular dysfunction in mouse model: head shaking and circling behavior. Inner ear malformation.	[111-114]

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