COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

Hiding in plain sight: genetic deaf-blindness is not always Usher syndrome

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Abstract Hearing loss (HL) is the most common congenital sensory impairment. Usher syndrome (USH) is the leading genetic etiology of congenital deafness combined with progressive vision loss, and individuals presenting with these symptoms are often assumed to have USH. This can be an erroneous assumption, as there are additional genetic causes of deaf-blindness. Our objective is to describe and accurately diagnose non-USH genetic causes of deaf-blindness. We present three children with hearing and vision loss with clinical and genetic findings suggestive of USH. However, ongoing clinical assessment did not completely support an USH diagnosis, and exome analysis was pursued for all three individuals. Updated genetic testing showed pathogenic variants in *ALMS1* in the first individual and *TUBB4B* in the second and third. Although HL in all three was consistent with USH type 2, vision impairment with retinal changes was noted by age 2 yr, which is unusual for USH. In all three the updated genotype more accurately fit the clinical phenotype. Because USH is the most common form of genetic deaf-blindness, individuals with HL, early vision impairment, and retinal dysfunction are often assumed to have USH. However, additional genes associated with HL and retinal impairment include *ALMS1*, *TUBB4B*, *CEP78*, *ABHD12*, and *PRPS1*. Accurate genetic diagnosis is critical to these individuals' understanding of their genetic conditions, prognosis, vision and hearing loss management, and future access to molecular therapies. If clinically or genetically USH seems uncertain, updated genetic testing for non-USH genes is essential.

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INTRODUCTION

Individuals with combined deaf-blindness constitute a small but diverse group (Anthony 2016). Estimates of the prevalence of deaf-blindness can range from 0.015% of the total population, with individuals under 18 years of age comprising 5.7% of this group, to 1.3% of the adult population (Lam et al. 2006; Wittich et al. 2012). Congenital deaf-blindness is rarer, presenting in an estimated 1 in 29,000 births (Dammeyer 2010). Etiologies of deaf-blindness across age groups include prenatal infection, prematurity, age-related causes, and genetic causes, with heritable causes estimated to be responsible in 27% of affected individuals (Wittich et al. 2012). The leading genetic etiology of deaf-blindness is Usher syndrome (USH), a form of hearing loss inherited in an autosomal recessive pattern with vestibular dysfunction and progressive vision loss. In one study of hard of hearing and deaf children, 11.3% had one or two pathogenic USH alleles, although in the affected individuals with a single

allele a second allele was not always identified (Kimberling et al. 2010). In a separate study of deaf-blind Canadian individuals aged from infancy to 105 years old, 20.9% of instances were attributable to USH based on clinical diagnosis (Wittich et al. 2012). Importantly, there are a number of other frequently overlooked genes associated with both hearing loss diagnosed in early childhood and visual impairment that may warrant distinct clinical management. Examples include *CEP78*, associated with cone-rod dystrophy and deafness; *SLC19A2*, associated with Leber's congenital amaurosis; and *PEX1* and *PEX6*, associated with Heimler syndrome (Srikrupa et al. 2014; Nikopoulos et al. 2016; Wangtiraumnuay et al. 2018).

Early and precise identification of deaf-blindness is critical so that interventions may begin that optimize the child's communication and cognitive and social–emotional development (Anthony 2016). Finding the true etiology of an individual's hearing and visual loss frequently requires genetic testing given similarities in clinical phenotypes across distinct forms of deaf-blindness in children. Furthermore, pinpointing an accurate genetic diagnosis will allow access to clinical trials of genetic therapies as they develop (Pan et al. 2017).

In this case study we present three individuals who were suspected to have USH from a clinical standpoint, despite the fact that in all three affected individuals, initial genetic testing did not completely support this diagnosis. Additional genetic evaluation was pursued for all three, identifying a definitive diagnosis that more accurately matched their clinical phenotype.

RESULTS

Individual 1

This 21-yr-old individual initially presented to Boston Children's Hospital (BCH) ophthalmology at 8 yr of age, although his vision impairments, nystagmus, and severe photophobia were initially diagnosed in his home country at 14 mo of age when he presented with "eye shaking." A brain magnetic resonance imaging (MRI) was completed in his home country at ~2–3 yr of age and was normal. His bilateral mild-moderate sensorineural hearing loss (SNHL), similar to his younger sister's, was reportedly detected incidentally at ~3–4 yr of age on a follow-up audiogram after an episode of acute otitis media. The diagnosis came as a surprise to the family as he spoke fluent English and two other languages. From an ophthalmologic standpoint, he had rod dystrophy, extreme photophobia, legal blindness, night blindness, and moderate to high frequency, low-amplitude horizontal nystagmus. He was "off balance" when walking heel-to-toe, although he participated in hockey and soccer when he was younger. Therefore, because of his early-onset visual impairment, hearing loss, and balance concerns a diagnosis of USH2 was considered. *USH2A* gene sequencing was completed, identifying two maternally inherited variants of unknown significance (Table 1). He also underwent testing for *GJB2*, which is the most common gene associated with nonsyndromic hereditary deafness and follows an autosomal recessive inheritance pattern. This testing identified a heterozygous pathogenic variant (Table 1). Because his younger sister had biallelic pathogenic variants in *GJB2* and mild congenital bilateral SNHL without vision loss, updated *GJB2* testing was pursued looking for a second allele, which was not identified. *MYO7A* gene sequencing and a Leber congenital amaurosis gene panel were also completed, both of which were negative (Table 1). Subsequent exome sequencing identified biallelic pathogenic variants in *ALMS1*, explaining both his hearing loss and retinal degeneration (Tables 2–4). Alström syndrome has wide phenotypic variability, although this individual lacked typical clinical features such as cardiomyopathy, developmental delay, and obesity. Currently, this young man's legal blindness and hearing loss are managed with dark glasses and hearing aids (Table 5). Because of his updated diagnosis, he is being monitored

Table 1. Genetic testing history

Individual	Test	Age at testing (yr)	Variants identified
1	*USH2A* gene sequencing	9	*USH2A* c.8656C > T p.(Leu2886Phe), heterozygous, maternally inherited *USH2A* c.9343A > G p.(Thr3115Ala), heterozygous, maternally inherited
1	*GJB2* gene sequencing	9	*GJB2* c.109G > A p.(Val37Ile), heterozygous, inheritance not reported
1	*MYO7A* gene sequencing	10	None
1	Leber's congenital amaurosis panel	10	None
1	Exome sequencing	19	*ALMS1* c.800G > A p.(Trp267*), heterozygous, maternally inherited *ALMS1* c.3902C > A p.(Ser1301*), heterozygous, paternally inherited
2	OtoSeq Tier 2	3	*WHRN* c.811delC p.(Leu277fs), heterozygous, inheritance not reported *GJB2* c.269T > C p.(Leu90Pro), heterozygous, inheritance not indicated *USH2A* c.7130A > G p.(Asn2377Ser), heterozygous, inheritance not reported *USH2A* c.13297G > T p.(Val4433Leu), heterozygous, inheritance not reported *USH2A* c.9343A > G p.(Thr3115Ala), heterozygous, inheritance not reported *PCDH15* c.5359C > T p.(Pro1787Ser), heterozygous, inheritance not reported
2	Targeted del/dup DFNB31, *GJB6, GJB2*	3	None
2	*USH2A* del/dup	6	None
2	NGS retinal dystrophy panel	6	*BBS7* c.1062_1063delTA p.(Tyr354Ter), heterozygous, inheritance not reported *WHRN* c.811delC p.(Leu277fs), heterozygous, inheritance not reported *GJB2* c.269T > C p.(Leu90Pro), heterozygous, inheritance not reported *USH2A* c.7130A > G p.(Asn2377Ser), heterozygous, inheritance not reported
2	Exome sequencing	6	*TUBB4B* c.1172G > A p.(Arg391His), heterozygous, de novo *WHRN* c.811delC p.(Leu277fs), heterozygous, de novo *GJB2* c.269T > C p.(Leu90Pro), heterozygous, paternally inherited *USH2A* c.7130A > G p.(Asn2377Ser), heterozygous, paternally inherited *USH2A* c.13297G > T p.(Val4433Leu), heterozygous, paternally inherited *USH2A* c.9343A > G p.(Thr3115Ala), heterozygous, paternally inherited *PCDH15* c.5359C > T p.(Pro1787Ser), heterozygous, maternally inherited
3	Targeted retinitis pigmentosa panel	7	*PRPH2* c.904G > A p.(Glu302Lys), heterozygous, paternally inherited *CACNA1F,* c.3811G > A p.(Val1271Ile), heterozygous, maternally inherited
3	Genome sequencing	8	*RGR* c.266C > A p.(Ser89*), heterozygous, inheritance not reported *PRPH2* c.904G > A p.(Glu302Lys), heterozygous, inheritance not reported *CACNA1F,* c.3811G > A p.(Val1271Ile), heterozygous, inheritance not reported
3	Exome and mitochondrial genome sequencing	9	*TUBB4B* c.1171C > T p.(Arg391Cys), heterozygous, de novo

Table 2. Exome sequencing results

Individual	Exome sequencing variants reported
1	*ALMS1* c.800G > A p.(Trp267*), heterozygous, maternally inherited *ALMS1* c.3902C > A p.(Ser1301*), heterozygous, paternally inherited
2	*TUBB4B* c.1172G > A p.(Arg391His), heterozygous, de novo *WHRN* c.811delC p.(Leu277fs), heterozygous, de novo *GJB2* c.269T > C p.(Leu90Pro), heterozygous, paternally inherited *USH2A* c.7130A > G p.(Asn2377Ser), heterozygous, paternally inherited *USH2A* c.13297G > T p.(Val4433Leu), heterozygous, paternally inherited *USH2A* c.9343A > G p.(Thr3115Ala), heterozygous, paternally inherited *PCDH15* c.5359C > T p.(Pro1787Ser), heterozygous, maternally inherited
3	*TUBB4B* c.1171C > T p.(Arg391Cys), heterozygous, de novo

Table 3. Molecular diagnoses

Individual	Gene (Transcript)	Coding DNA	Amino acid change	Classification	ACMG/AMP criteria applied	Pure tone average[a] of most recent audiogram		Age at most recent audiogram (yr)
1	*ALMS1* (NM_015120.4)	c.800G > A	p.(Trp267*)	Pathogenic (Astuti et al. 2017)	PM2, PVS1, PP4	45 (L)	47.5 (R)	21
		c.3902C > A	p.(Ser1301*)	Pathogenic (Yang et al. 2017)	PM2, PVS1, PP4			
2	*TUBB4B* (NM_006088.6)	c.1172G > A	p.(Arg391Hi)s	Pathogenic (Luscan et al. 2017)	PS2, PM2, PM5, PS3_Supporting, PP1, PP3	35 (L)	32.5 (R)	6
3	*TUBB4B* (NM_006088.6)	c.1171C > T	p.(Arg391Cys)	Pathogenic (Luscan et al. 2017)	PS2, PM2, PM5 PS3_Supporting, PP3	48.8 (L)	46.3 (R)	8

[a]Pure Tone Average calculated as an average of 500-Hz, 1000-Hz, 2000-Hz, and 4000-Hz hearing thresholds in masked bone conduction, in dB.

for other features of Alström syndrome including cardiomyopathy, insulin resistance, hyperlipidemia, endocrine abnormalities, hepatic disease, and obesity.

Individual 2

Individual 2 presented to BCH ophthalmology at age 5 yr and 7 mo upon concerns about worsening low vision. She passed her newborn hearing screening "on the third or fourth try" according to the medical record and began walking at 15 mo, although it is consistently documented that she was clumsy. Her hearing loss was detected at 3 yr of age after she failed her otoacoustic emission screening at school. She was confirmed to have mild-moderate bilateral SNHL, which was worse at the higher frequencies (1000–8000 Hz bilaterally), and she began using hearing aids (Fig. 1). Concerns for her vision arose before her second birthday when her parents noticed her bumping into a wall. It was noted that she bumped into things around her periphery and had difficulty seeing steps before she descended. She began wearing glasses at 2.5 yr of age. At 6 yr, she was found to have elevated dark adapted thresholds, and nystagmus was clinically documented and described as intermittent, low-amplitude, and low-moderate frequency. Hearing loss panel testing at age 4 yr identified

Table 4. Variant information

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/dbVar ID	Genotype	ClinVar ID	Parent of origin
ALMS1	Chr 2: 73424462	c.800G>A	p.(Trp267*)	Single-nucleotide variant	Nonsense	rs1558639105	Heterozygous	VCV000620305	Maternally inherited
ALMS1	Chr 2: 73450426	c.3902C>A	p.(Ser1301*)	Single-nucleotide variant	Nonsense	rs769219669	Heterozygous	VCV000264657	Paternally inherited
TUBB4B	Chr 9: 137243390	c.1172G>A	p.(Arg391His)	Single-nucleotide variant	Missense	rs1554786803	Heterozygous	VCV000492938	De novo
TUBB4B	Chr 9: 137243389	c.1171C>T	p.(Arg391Cys)	Single-nucleotide variant	Missense	rs1554786802	Heterozygous	VCV000492939	De novo

Table 5. Most recent Boston Children's Hospital ophthalmologic data

Individual 1 [*ALMS1*]		
Corrected visual acuity		
Right	Left	Both
20/250	20/250	20/250
Current glasses	Right Left	+3.75 +2.50 × 100 +3.50 +2.75 × 94
Individual 2 [*TUBB4B*]		
Corrected visual acuity		
Right	Left	Both
20/500	20/200	20/150
Current glasses	Right Left	+7.50 +2.00 × 90 +5.75 +2.00 × 90
Individual 3 [*TUBB4B*]		
Corrected visual acuity		
Right	Left	Both
20/250	20/300	20/200
Current glasses	Right Left	+7.50 +1.0 × 90 +7.50 +1.00 × 90

a heterozygous pathogenic frameshift variant in *WHRN*, the gene for Usher syndrome 2D, and although the disorder associated with this gene follows a recessive inheritance pattern and only one variant was identified, she was assumed to have USH (Table 1). A heterozygous variant of uncertain significance in *USH2A* was also identified, as well as two likely benign variants in this gene (Table 1). Subsequent exome sequencing (trio with both parents) identified a de novo variant of uncertain significance (c.1172G > A) in *TUBB4B* (Tables 1 and 2). Parentage was confirmed with multiple rare variants in the trio. At age 8 yr, an updated literature search identified a publication describing the same *TUBB4B* variant in several unrelated individuals with a similar phenotype and classified the variant as pathogenic (Luscan et al. 2017). Therefore, this individual's vision and hearing loss are now attributed to the *TUBB4B* variant (Tables 3 and 4).

Individual 3

This now 10-yr-old boy presented to BCH ophthalmology, otolaryngology, and genetics at age 8 yr for an evaluation of vision and hearing problems detected in his home country. He was diagnosed with bilateral SNHL at age 8 mo after failing his newborn hearing screen, and he started wearing hearing aids shortly thereafter. Audiometric evaluation at BCH identified bilateral mild to moderate SNHL (Fig. 1). An MRI of the brain and temporal bones was also completed at BCH and was normal. From a vision standpoint, he was first diagnosed with severe amblyopia and night blindness at 2 yr of age in his home country after his parents noticed that he would frequently rub his eyes, squint, turn his head, and cry in the dark. He seemed to be off balance when he walked at 18 mo, and his parents reported that he fell frequently, struggled with sports, and had difficulty navigating unfamiliar areas. Ophthalmologic evaluation at BCH confirmed a diagnosis of advanced retinal degeneration and constricted visual fields. Genetic diagnoses including USH and Alström syndrome were initially suspected in his home country; however, targeted sequencing of genes associated with retinitis pigmentosa and genome sequencing were completed in his home country and were unrevealing for either of these syndromes (Table 1). Subsequent exome and

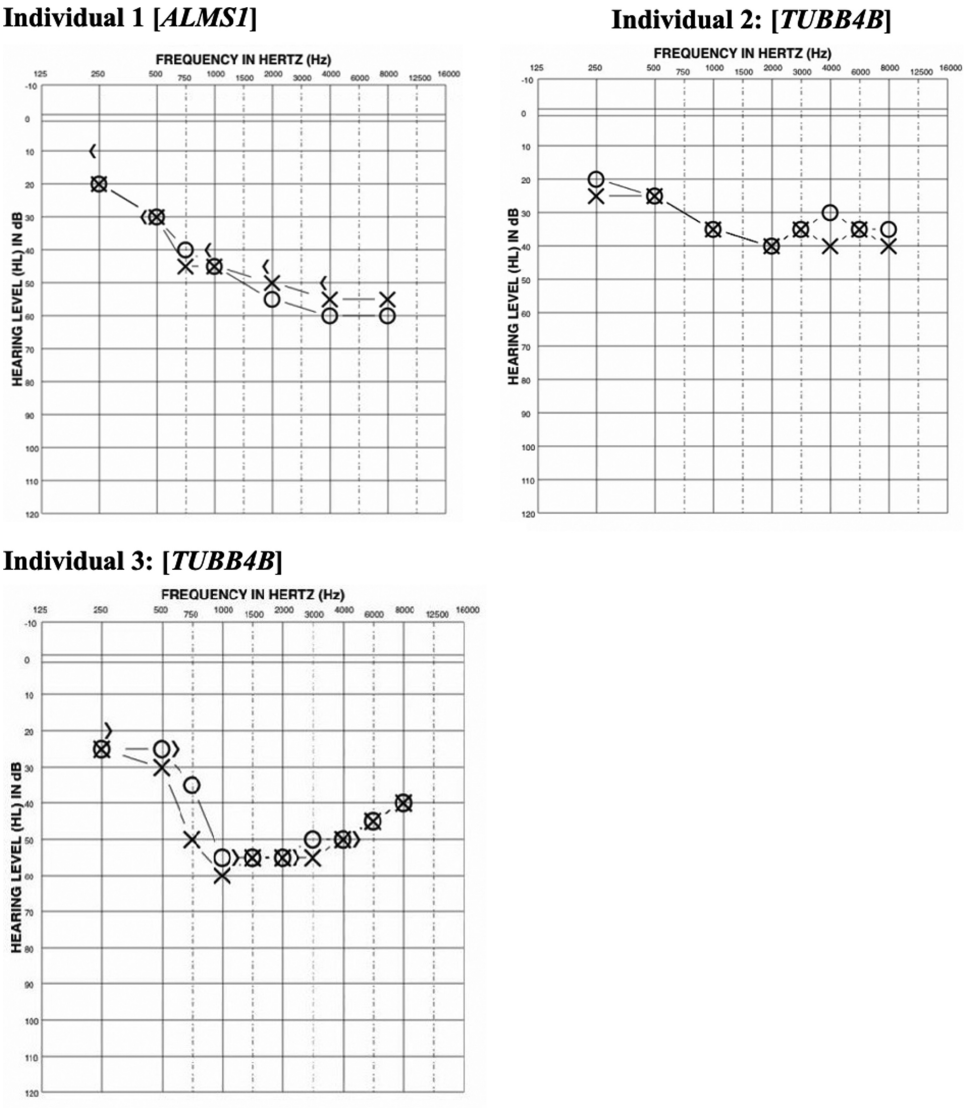

Figure 1. Most recent Boston Children's Hospital audiograms. Audiograms represented by symbols. Right ear unmasked air conduction represented by ○. Left ear unmasked air conduction represented by ×. Unmasked bone conduction of the right ear is represented by <. Unmasked bone conduction of the left ear is represented by >.

mitochondrial genome sequencing ordered at BCH identified a de novo variant in the *TUBB4B* gene, which had not been reported in the results of the prior genome sequencing that he underwent in his home country (Table 1). Parentage was confirmed with multiple rare variants in the trio. The variant was determined to be the cause of his hearing loss and retinal degeneration (Tables 3 and 4). His vision impairment and SNHL are currently managed with glasses, hearing aids, and classroom accommodations (Table 5). In addition, the family has been counseled on the suspected autosomal dominant inheritance of the apparently de novo variant, and they have been encouraged to join parent support groups that may facilitate their access to clinical trials for Leber's congenital amaurosis with early-onset deafness if any become available.

DISCUSSION

Pediatric deaf-blindness is a critical finding, necessitating personalized auditory habilitation and services to ensure optimization of communication, cognitive development, and quality of life. Causes of pediatric deaf-blindness include prenatal infection, complications of prematurity, and genetic syndromes, with genetic causes accounting for an estimated 27% of deaf-blindness in the overall population (Wittich et al. 2012). Although USH is the most common form of genetic deaf-blindness, the early and correct identification of non-USH genetic causes of deaf-blindness is of critical importance as this information will inform the prognosis of hearing and vision loss progression as well as access to clinical trials for molecular therapies. Additionally, non-USH genetic causes of deaf-blindness can manifest with additional clinical features ranging from premature aging to diabetes and heart disease, making their early and precise identification of clinical importance.

Other genetic syndromes significantly affecting hearing and vision include CHARGE syndrome, Heimler syndrome, Norrie's disease, *OPA1* variants, Kearns–Sayre syndrome (KSS), Alström syndrome, *EXOSC2* variants, and *CEP78* variants, among others (Table 6). In many instances, children initially present with USH-like features, delaying the benefits of a more accurate diagnosis. Heimler syndrome, caused by *PEX6* and *PEX1* variants causing issues with fatty acid breakdown, has also been reported to present with USH-like symptoms initially (Wangtiraumnuay et al. 2018). In one case series, SNHL and amelogenesis imperfecta were the first symptoms, with vision issues noticed in later childhood (Wangtiraumnuay et al.

Table 6. Frequently overlooked deaf-blind genes

	Gene	Inheritance Pattern	Phenotype	Estimated prevalence
Alström syndrome (Alström et al. 1959)	*ALMS1* (Hearn et al. 2002)	Autosomal recessive (Marshall et al. 2007)	Gradual vision and hearing loss in childhood, obesity, and heart disease	1:100,000-1:1,000,000 (Paisey et al. 2019)
Cone-rod dystrophy and hearing loss	*CEP78* (Nikopoulos et al. 2016)	Autosomal recessive (Nikopoulos et al. 2016)	Cone-rod dystrophy with postlingual hearing loss	
Short stature, hearing loss, retinitis pigmentosa, and distinctive facies	*EXOSC2* (Di Donato et al. 2016)	Autosomal recessive (Di Donato et al. 2016)	Retinitis pigmentosa, premature aging, short stature, intellectual disability, hearing loss, distinctive facies	
Heimler syndrome (Heimler et al. 1991; Wangtiraumnuay et al. 2018)	*PEX1; PEX6* (Ratbi et al. 2015)	Autosomal recessive	Sensorineural hearing loss associated with retinal pigmentation and amelogenesis imperfecta	29 affected individuals have been reported (Gao et al. 2019)
Stickler syndrome (Khalifa et al. 2014)	*COL2A1* (Francomano et al. 1987); *COL11A1* (Sirko-Osadsa et al. 1996); *COL11A2* (Sirko-Osadsa et al. 1998); *COL9A1* (Van Camp et al. 2006); *COL9A2* (Baker et al. 2011); *COL9A3* (Faletra et al. 2014)	Autosomal recessive and autosomal dominant	Deafness, myopia/cataracts, midface hypoplasia, early-onset arthritis	1:7500–1:9000 (Robin et al. 2017)

(*Continued on next page.*)

Table 6. (*Continued*)

	Gene	Inheritance Pattern	Phenotype	Estimated prevalence
Norrie's disease (Warburg 1966)	*NDP* (Meindl et al. 1992)	X-linked recessive (Caballero et al. 1996)	Blindness in male infants at birth, abnormal retinal development, 25%–33% develop hearing loss, classically associated with intellectual disability (Warburg 1966)	More than 400 affected individuals have been reported (Huang et al. 2017)
Optic atrophy with hearing loss	*OPA1* (Wissinger et al. 2000; Roubertie et al. 2015)	Autosomal dominant (Roubertie et al. 2015)	Childhood-onset moderate visual loss. SNHL reported in ~27% of affected individuals (Roubertie et al. 2015)	At least 1:35,000 (Yu-Wai-Man et al. 2010)
Ophthalmoplegia (CPEO)/ Kearns–Sayre syndrome (KSS) (Kearns 1965) (Kornblum et al. 2005)	Mitochondrial DNA deletions (Kornblum et al. 2005)	Mitochondrial	Progressive ophthalmoplegia, pigmentary retinitis, with deafness as a common additional feature (Kornblum et al. 2005)	About 1.6:100,000 (Shemesh and Margolin 2020)
PHARC (Fiskerstrand et al. 2009)	*ABHD12* (Torunn Fiskerstrand et al. 2010)	Autosomal recessive (Frasquet et al. 2018)	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, cataract	
Arts syndrome (Arts et al. 1993)	*PRPS1* (de Brouwer et al. 2010)	X-linked, recessive (Almoguera et al. 2014)	Sensorineural deafness associated with optic atrophy, peripheral neuropathy, hypotonia; female carriers may experience symptoms, but generally much milder phenotype	Four affected kindreds have been reported (de Brouwer and Christodoulou 2018)
Retinitis pigmentosa, X-linked, and sinorespiratory infections, with or without deafness	*RPGR* (Zito et al. 2003)	X-linked, recessive (Zito et al. 2003)	Involved in cilia function, variants may lead to retinitis pigmentosa, with instances of reported hearing loss as well	
Senior–Loken syndrome (Senior et al. 1961; Loken et al. 1961; Clarke et al. 1992)	*NPHP1* (Caridi et al. 1998); *IQCB1* (Otto et al. 2005); *SDCCAG8* (Otto et al. 2010); *WDR19* (Coussa et al. 2013); *CEP290* (Sayer et al. 2006)	Autosomal recessive	Disease associated with sensorineural hearing loss, renal system dysfunction, and retinal dystrophy and also nystagmus	1:1,000,000 (Otto et al. 2005)
Leber's congenital amaurosis with early onset deafness	*TUBB4B* (Luscan et al. 2017)	Autosomal dominant (Luscan et al. 2017)	Early onset retinal degeneration and mild-moderate hearing loss	
Wolfram syndrome (Wolfram and Wagener 1938; Dhalla et al. 2006)	*WFS1* (Inoue et al. 1998)	Autosomal recessive	Childhood onset diabetes mellitus, optic atrophy and deafness	More than 90 affected individuals from more than 60 families described worldwide (Tranebjærg et al. 2020)

2018). Wolfram syndrome, although associated with a range of symptoms in addition to deaf-blindness including diabetes, ataxia, and neuropathy, has also been reported to present initially with diabetes, neurogenic bladder, and high-frequency hearing loss in childhood and decreasing vision and night vision in late childhood/early adolescence (Dhalla et al. 2006). Stickler syndrome is a connective tissue disorder characterized by sensorineural hearing loss, progressive myopia, midface underdevelopment, and early-onset arthritis that can have significant intrafamilial variability (Robin et al. 2017).

RPGR variants, associated with X-linked inheritance, which manifest retinitis pigmentosa, hearing loss, sinusitis, and chronic respiratory tract infection, also shares many phenotypic features with USH (Zito et al. 2003). In a case report of one individual with Leber's congenital amaurosis, typically associated with poor vision, SNHL, diabetes mellitus, and megaloblastic anemia, poor vision and hearing loss were noted by 1 yr of age, whereas anemia and diabetes were noticed later (Srikrupa et al. 2014). Although it is challenging to differentiate these genetic syndromes from USH at early ages based on clinical presentation alone, an accurate diagnosis is crucial to families and clinicians as it will guide audiologic and ophthalmologic habilitation and prepare the family for complications such as anemia and diabetes.

In the case of Individual 2, her reported clumsiness, hearing loss, retinal degeneration, and heterozygous pathogenic variant in *WHRN* suggested a diagnosis of Usher syndrome type 2D. However, the early onset, rapid rate of progression, and generalized nature of her retinal degeneration, more consistent with Leber's amaurosis, and relatively mild hearing loss prompted reassessment of her multiple previous genetic studies. The updated diagnosis of a pathogenic variant in *TUBB4B* matches her phenotype much better than her previously considered diagnosis of USH2D. A publication by Luscan et al. (2017) was critical to the identification of the cause of her deaf-blindness, as it is the first to report pathogenic variants in this gene as causative for this phenotype. In this paper, five individuals (three unrelated) had the same point variants causing the same protein level change in the *TUBB4B* gene as Individual 2, and all had similar clinical phenotypes. It is hypothesized to be inherited in an autosomal dominant manner, manifesting as early-onset and severe photoreceptor and cochlear cell loss coupled with hearing loss (Luscan et al. 2017).

Individual 3's hearing loss, retinal degeneration, and difficulties walking and navigating were suggestive of USH; however, genetic testing in his home country was unrevealing. When he presented to BCH genetics, USH2 was still considered as a potential diagnosis, but it was noted that his retinitis pigmentosa was detected earlier (age 2 yr) than is typical for USH2 (generally later in childhood or teenage years). The individual's current clinical diagnosis of Leber's congenital amaurosis is a more accurate phenotypic match for his early-onset retinal degeneration. The Luscan et al. (2017) publication that supported a diagnosis for Individual 2 was critical to the diagnosis of this individual as well. The publication describes one individual with an identical point variant and protein change in *TUBB4B* as the one detected in Individual 3 with a similar clinical presentation of early-onset retinal degeneration and SNHL (Luscan et al. 2017). The variants identified in Individuals 2 and 3 add two new associations of *TUBB4B* variants and deaf-blindness to a growing literature. Furthermore, the presence of vestibular symptoms in both of these individuals suggests a vestibular component to Leber's congenital amaurosis, which was not described in the Luscan et al. publication. Finally, the clinical ophthalmologic manifestations of Leber's congenital amaurosis have been linked to more than an additional dozen genes, some of which may also be associated with hearing loss (Kondkar and Abu-Amero 2019).

Other deaf-blind phenotypes often have other more recognizable symptoms in their classic presentation; however, because of variable presentation of genetic syndromes, they may also initially appear to be USH. PHARC syndrome, characterized by polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataracts, is notable for its variable age

at onset of polyneuropathy (Frasquet et al. 2018). Norrie's disease, caused by a variant on the X chromosome, frequently presents as congenital retinal degeneration and proliferation which progresses to retinal detachment, with hearing loss manifesting in a roughly estimated 25%–33% of these individuals (Caballero et al. 1996; Warburg 1966). *PRPS1* variants result in three distinct disorders, all of which present with hearing loss as a common feature (Almoguera et al. 2014). A recent molecular discovery is a genetic syndrome characterized by hearing loss, myopia, retinitis pigmentosa, and hypothyroidism among other symptoms has been attributed to *EXOSC2* variants resulting in mutation of an RNA exosome cap protein (Di Donato et al. 2016).

Atypical clinical presentations can also lead to an incorrect diagnosis. Individual 1 did not fit the typical Alström phenotype; he was tall and slender and had no endocrine or cardiac issues throughout childhood and adolescence. However, the Alström phenotype is highly variable. Astuti et al. (2017) describe one individual with the same p.Trp267* variant as Individual 1's; this individual's clinical features included vision impairment, cardiomyopathy, hemiparesis, and normal hearing. The publication that first identified the p.Ser1301* variant that was also identified in Individual 1 notes that the affected individual did not meet the clinical criteria for diagnosis of Alström syndrome (Yang et al. 2017). In the case of Individual 1, his hearing loss was similar to his sister's, but he only had one pathogenic *GJB2* variant. His progressive vision loss suggested USH, but genetic testing was negative for the tested USH genes. His Alström diagnosis more accurately fits his retinal and audiologic phenotype and will support close monitoring for signs of cardiomyopathy and insulin resistance.

The clinical courses of these three individuals underscore the importance of genetic testing, in particular exome sequencing, in the workup of children with congenital SNHL and vision loss that is not attributable to USH. Persistence on the part of these three families and care teams in pursuing both updated genetic testing and literature searches were key to receiving these molecular confirmations. If clinical or genetic suspicion of USH seems uncertain, updated exome sequencing should be considered as an incorrect USH diagnosis may preclude access to appropriate prognostic information and clinical management. As the rate of discovery of hearing loss genes continues to accelerate, we expect that comprehensive genetic evaluations of pediatric deaf-blindness will increasingly yield positive results that will inform audiologic and ophthalmologic management and allow providers to anticipate other reported medical needs for children with these distinct genetic syndromes. An accurate genetic diagnosis will also potentially make these individuals eligible for clinical trials for genetic therapies in the future.

METHODS

Genetic testing was ordered by physicians, and sequencing was completed at diagnostic laboratories (Supplemental Table 1).

ADDITIONAL INFORMATION

Data Deposition and Access

The ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) accession numbers for these three individuals are as follows:

Individual 1

USH2A c.8656C > T p.(Leu2886Phe): VCV000048607

USH2A c.9343A > G p.(Thr3115Ala): VCV000048623

GJB2 c.109G > A p.(Val37Ile): VCV000017023
ALMS1 c.800G > A p.(Trp267*): VCV000620305
ALMS1 c.3902C > A p.(Ser1301*): VCV000264657
Individual 2
WHRN c.811delC p.(Leu277fs): not reported in ClinVar
GJB2 c.269T > C p.(Leu90Pro): VCV000017016
USH2A c.7130A > G p.(Asn2377Ser): VCV000048577
USH2A c.13297G > T p.(Val4433Leu): VCV000048415
USH2A c.9343A > G p.(Thr3115Ala): VCV000048623
PCDH15 c.5359C > T p.(Pro1787Ser): VCV000046498
BBS7 c.1062_1063delTA p.(Tyr354Ter): not reported in ClinVar
TUBB4B c.1172G > A p.(Arg391His): VCV000492938
Individual 3
RGR c.266C > A p.(Ser89*): not reported in ClinVar
PRPH2 c.904G > A p.(Glu302Lys): not reported in ClinVar
CACNA1F, c.3811G > A p.(Val1271Ile): not reported in ClinVar
TUBB4B c.1171C > T p.(Arg391Cys): VCV000492939

Raw sequencing data could not be deposited because of lack of patient consent.

Ethics Statement

This study was approved as a retrospective chart review by the BCH Institutional Review Board (IRB-P00000307).

Competing Interest Statement

The authors have declared no competing interest.

Referees

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Author Contributions

G.M. and J.P. performed data collection and manuscript drafting, and reviewed the final manuscript as submitted. A.O. confirmed the genetic diagnoses of this cohort, assisted in manuscript drafting and editing, and reviewed the final manuscript as submitted. M.K. conceptualized this study, assisted in manuscript drafting and editing, and approved the final manuscript as submitted. All authors have approved the current version of the manuscript and its submission to *Cold Spring Harbor Molecular Case Studies*.

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