Inherited Causes of Combined Vision and Hearing Loss: Clinical Features and Molecular Genetics

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ABSTRACT

Combined vision and hearing loss, also known as dual sensory impairment, can occur in several genetic conditions, including ciliopathies such as Usher and Bardet-Biedl syndrome, mitochondrial DNA disorders and systemic diseases, such as CHARGE, Stickler, Waardenburg, Alport and Alstrom Syndrome. The retinal phenotype may point to the diagnosis of such disorders. Herein, we aim to provide a comprehensive review of the molecular genetics and clinical features of the most common non-chromosomal inherited disorders to cause dual sensory impairment.

Keywords:

Dual sensory impairment, hearing loss, retinitis pigmentosa, Usher syndrome, Bardet-Biedl syndrome, retinal dystrophy

INTRODUCTION

Combined hearing and vision loss, also known as dual sensory impairment (DSI), can be caused by a highly heterogenous spectrum of conditions and is characterised by varying degrees of hearing and vision loss. DSI is common in older adults, with a prevalence as high as 11.3% in adults over 80 years of age in the US [1]. Regardless of the cause, affected individuals experience difficulty in communication, mobility and daily functioning [2], and perceived discrimination [3].

There are many causes of DSI, including genetic [4], infectious [5], and auto-immune [6-8]. Genetic causes of DSI usually present as early as birth to early adulthood, associated with a greater disease burden and lifelong disability. Ciliopathies [9-13], CHARGE [14, 15], Waardenburg [16], Stickler [17, 18], Kearns-Sayre [19], and albinism-deafness syndromes [20], are some of the commonest genetic causes of DSI that may present to an ophthalmologist. The differential diagnosis may be explored via a detailed ocular and medical history, family history, symptomatology, examination, retinal imaging and electrophysiological assessment, audiology and, ultimately, molecular genetic testing. Furthermore, recent advances in the gene therapy and cell replacement field offer a promising treatment option for the future, with many pre-clinical and human trials being developed or currently ongoing [21-23].

The purpose of this review is to provide an overview of the most common genetic causes of combined hearing and vision loss, outlining the ocular manifestations, with a focus on the retinal findings. Description of syndromes secondary to chromosomal abnormalities is beyond the scope of this review. **Table 1** provides a summary of the molecular genetics of all conditions described herein.

1. CILIOPATHIES

The primary cilia are rod-like, slender, ancient microscopic organelles that have an evolutionarily conserved intraflagellar transport (IFT) mechanism and exert a crucial role in signal transduction cascades [24] and vertebrate development [25]. Genetic disorders that cause disruption in the primary cilium, known as ciliopathies, display a constellation of phenotypic features, commonly involves sensory deficits and is a leading cause of visual disability in children [26]. Below we review the phenotype and genetics of the most common ciliopathies that exhibit retinal findings.

Usher syndrome

Usher syndrome (USH) refers to a genetically and clinically heterogenous group of recessively inherited disorders, characterised by DSI with or without vestibular dysfunction. It is the leading cause of inherited DSI, with a prevalence ranging from 1-4 per 25,000 [9]. The disease is classified into four subtypes (USH1, USH2, USH3 and USH4), with wide intra- and inter-familial phenotypic heterogeneity [27]. Some USH-related genes have also been associated with isolated retinitis pigmentosa (RP) and non-syndromic hearing loss. The visual prognosis varies with the subtype of USH, with USH1 individuals experiencing an earlier onset of nyctalopia and more rapid decline in visual function with age [28]. **Figure 1** illustrates the retinal, optical coherence tomography (OCT) and fundus autofluorescence (FAF) findings in representative patients of USH1, USH2 and USH3. Imaging findings in USH4 are described in the relevant subsection below. Rod-cone dystrophy develops in all cases, although with varying age of onset depending on the subtype, while cystoid macular oedema and cataracts are a relatively common feature and may be present in more than 50% of all cases [29].

USH1

USH1 is the most severe form of USH and accounts for 30-40% of all USH [30]. Patients with USH1 have profound - and typically congenital - sensorineural hearing loss, vestibular dysfunction and onset of RP within the first decade of life [11]. Unless fitted with cochlear implants, affected individuals do not typically develop speech [31]. Eight loci have been associated with USH1 (Table 1), with five genes identified to date [9, 32-34] - the most common being *MYO7A* (USH1B; OMIM #276903) [35-37]. *CIB2* (OMIM #605564) was previously associated with USH1 [38], but more recent evidence disqualified the gene as causative of the disease [39].

USH2

USH2 is the commonest form of USH, with moderate to severe early-onset sensorineural hearing loss, with intact to variable vestibular responses [40], and onset of RP within the second decade of life. In a study of 560 USH families, 59% had USH2 [41]. In one study, the mean age of onset of hearing loss in patients with USH2 was 11 years of age [28]. Three disease-causing genes have been identified [9]. In a UK study, *USH2A* (OMIM #608400) was the most commonly involved gene in USH2, found in 79% of cases. This gene is also the commonest cause of autosomal recessive (AR) non-syndromic RP [42]. The most prevalent *USH2A* variant is c.2299delG, with one study reporting frequencies as high as 77.5% in patients with USH2 [43] - and likely represents an ancestral mutation that spread worldwide as a result of migration [44].

USH3

USH3 is the rarest subtype and exhibits later onset of progressive hearing and progressive vision losses. It is typically associated with vestibular hyporeflexia. [45]. Affected individuals have normal speech and will gradually become profoundly deaf. The onset of RP is usually post pubertal, with subsequent constriction of visual fields and nyctalopia [46, 47]. Although prevalence is variable, it accounts for 1-6% of USH cases [45, 48], except in the Finnish and Ashkenazi Jewish population [49], where it is estimated that more than 40% of patients with USH have USH3 [50, 51]. USH3 is primarily caused by pathogenic variants in *CLRN1* (OMIM #606397) [51], which encodes clarin-1, a vertebrate-specific protein containing four transmembrane domains and suggested to be involved in hair cell and photoreceptor cell synapses [52]. Variants in *HARS1* (OMIM #142810) have been previously associated with USH3 [53], although a recent expert curation of genes related to hearing loss refuted and disqualified *HARS1* as causative of USH3 [54].

USH4

An atypical subtype of USH (USH4) has been associated with disease-causing variants in *ARSG* (OMIM #618144) [55]; with the genetic spectrum recently expanded to include *CEP78* (OMIM #617110)*, CEP250* (OMIM #609689) and *ABHD12* (OMIM #613599) [56]. This form is rare and atypical in that there is a later onset - usually around 40 years of age - of RP and sensorineural hearing loss without vestibular involvement [57]. In most reported cases, a sharply demarcated region(s) of pigmentary change in the fundus, with optic disc pallor, and parafoveal and mid-peripheral retinal pigment epithelium (RPE) atrophy are observed. FAF may

reveal a perimacular hyperautofluorescent ring or a pericentral pattern of hypoautofluorescence. Intraretinal cystoid spaces may be present on OCT [58, 59].

Bardet-Biedl syndrome

Bardet-Biedl syndrome (BBS) is a multi-systemic disease characterized by pan-retinal rod-cone degeneration, renal dysfunction, obesity, hypogonadism, postaxial polydactyly and cognitive impairment [60, 61]. It is typically inherited in an AR fashion; although a tri-allelic mechanism of transmission has been reported [62]. Retinal abnormalities are seen in virtually all patients - in a large multi-ethnic cohort of 105 cases, signs of retinal dystrophy were seen in all patients older than 3 years of age [63]. The visual prognosis is often poor, with legal blindness occurring before the second decade of life [64, 65]. More commonly, patients may develop a conductive hearing loss, secondary to chronic otitis media, although sensorineural hearing loss can also occur [60].

The retina exhibits a wide spectrum of disease expression [66], varying from generalised rod-cone to cone-rod dysfunction, often with early macular involvement. Disease severity and retinal findings may vary among members of the same family [66, 67]. The fundus usually reveals pale optic discs, vessel attenuation and diffuse RPE mottling, while OCT shows atrophy of the ellipsoid zone and RPE [68] (**Figure 2**). Studies have been contradictory regarding specific genotype-phenotype correlations in BBS [69-76].

To date, twenty-two disease-causing genes have been identified (**Table 1**), of which eight are highly conserved genes that code for BBS proteins. These BBS proteins form a stable complex that has a role in membrane trafficking and as a key regulator of the composition of transmembrane proteins in the ciliary membrane,

known as the BBSome [77]. *BBS1* and *BBS10* account for about 50% of BBS cases, while variants in the BBsome-related genes (*BBS1*-*BBS18*) are responsible for approximately 70 to 80% of affected families [78], with several of these having a high prevalence in certain populations, demonstrating founder effects and the worldwide genetic heterogeneity of BBS [79]. Preclinical work is being undertaken to develop gene therapy approaches for several BBS genotypes, including *BBS1* and *BBS10*.

Alstrom syndrome

Alstrom syndrome (ALMS) is a multi-systemic AR disorder characterized by retinal degeneration, hearing loss, childhood obesity, diabetes mellitus, urological dysfunction, dilated cardiomyopathy, systemic fibrosis, and renal, pulmonary and hepatic failure [80, 81]. The prevalence of ALMS in the general population is estimated to be less than 1:1,000,000 [82]. The cause of ALMS is pathogenic variants in *ALMS1* (OMIM # 606844), a gene involved in centriole formation and stability, with a role in intracellular trafficking and ciliary function [83-86].

A genotype-phenotype study (n=58) by Marshall et al., found possible associations between pathogenic variants in exon 16 and onset of retinal degeneration before 1 year of age, as well as the occurrence of urological dysfunction, diabetes and dilated cardiomyopathy. A significant association was also found between variants in exon 8 and lower incidence of renal disease [80]. Progressive bilateral sensorineural hearing loss is often found in the first decade of life and may be a feature in up to 90% of affected individuals. This can become moderate to severe in nature by the second decade of life. Chronic and acute otitis media can also cause a conductive component to the hearing loss [82, 87].

ALMS usually presents with severe cone-rod dystrophy, diffuse vessel attenuation, optic disc pallor and macular atrophy (**Figure 3-A**). Nystagmus and extreme photophobia, with or without nyctalopia, are characteristic, with an age of symptom onset at 6 to 9 months old, a combination of symptoms that may mislead to the diagnosis of Leber congenital amaurosis, achromatopsia or Bardet-Biedl syndrome [88]. The visual prognosis is very poor and complete blindness usually occurs in the second decade of life [89]. FAF may show hypoautofluorescent patches with a parafoveal hyperautofluorescent ring [88], while OCT reveals foveal and outer nuclear layer (ONL) thinning accompanied by loss of photoreceptors and RPE [90]. ERG reveals generalised retinal dysfunction within a few weeks of birth, with extinguished cone and rod-based responses by 2.5 years of age [82]. However, variability in retinal function, disease onset and rate of progression have been reported [88, 91]. Other eye findings that may be present are hypermetropia and subcapsular cataracts [88].

2. Auditory-pigmentary Syndromes

Tietz albinism-deafness syndrome

Tietz albinism-deafness syndrome (TS) is characterised by congenital sensorineural hearing loss and generalised loss of pigmentation. It was first described in a family in 1963 [92], which was subsequently found to segregate variants in *MITF* (OMIM #156845) [20], a gene involved in differentiation, growth and survival of pigment cells [93, 94]. Disease-causing variants in *MITF* may more commonly cause AD Waardenburg syndrome type 2 (WS2) [95, 96] and, rarely, AR coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism and deafness syndrome

(COMMAD) [97]. The WS2 phenotype highly overlaps with TS but is distinguishable given TS has a more severe phenotype; with patchy depigmentation, heterochromia irides and white forelocks [92, 98].

TS individuals are born "snow white", gradually gaining pigmentation, with adults having fair skin, blonde to white hair and white eyelashes and eyebrows. The hearing loss is bilateral, sensorineural, congenital and profound, with speech rarely developing [20, 99]. Individuals have blue eyes and a diffuse lack of retinal pigmentation, although, interestingly, there are no other ocular abnormalities such as nystagmus, photophobia or other visual problems as seen in other conditions characterised by blonde fundi [20, 92, 99, 100].

Waardenburg syndrome

Waardenburg syndrome (WS) is a genetically heterogenous auditory-pigmentary syndrome that was first described in 1951, with an estimated prevalence of 1 per 42,000 [101]. Nine loci have been identified so far and. WS is often inherited in an AD fashion, but AR inheritance has also been described. Interestingly, Wollnik et al reported a family in which parents were heterozygous for the substitution p.Y90H in the *PAX3* gene (OMIM #606597) and had WS subtype 1 (WS1), while the offspring was homozygous for the variant and had subtype 3 (WS3), which highlights different inheritance patterns in the same gene and within family members [102]. Based on the phenotype, it can be classified in four main groups, the first two being the commonest [98]: (i) WS1 is characterised by pigmentary abnormalities of hair, which include a very characteristic white forelock, pigmentary changes of the iris, sensorineural hearing loss and dystopia canthorum; (ii) WS2 has a similar phenotype, but without dystopia canthorum; (iii) WS3 has the same features as

WS1, including dystopia canthorum, but also musculoskeletal abnormalities of upper limbs; and (iv) WS4 has pigmentary changes and Hirschsprung disease of the colon [98, 103].

The hearing loss is typically bilateral, although with variable intra- and interfamilial expression [104]. It occurs in about 25% of patients affected with WS1 and in half of the patients with WS2 [105]. The pattern of iris pigmentation varies from brown iris, to sectoral patches of hypopigmentation to classical heterochromia irides [106]. The fundus often reveals pigmentary changes, varying from a blonde fundus, to blonde areas adjacent to patchy hyperpigmented areas [106]. FAF may reveal hypoautofluorescence in the region of choroidal hypopigmentation, while OCT may demonstrate a thickened choroid in the area of hypopigmentation, with an otherwise normal overlying retina [107, 108].

3. Mitochondrial Disorders

Kearns-Sayre syndrome

Kearns-Sayre syndrome (KSS) is a rare multi-system mitochondrial DNA (mtDNA) deletion syndrome [109, 110], characterised by chronic progressive external ophthalmoplegia, pigmentary retinopathy and heart block [110]. Several other features have been reported, such as sensorineural hearing loss, cerebellar ataxia, endocrine disorders, cognitive impairment, and increased levels of cerebrospinal fluid protein [19, 111-114]. A study by Kornblum et al. assessed the nature of the hearing loss in 17 affected individuals, 10 of whom were found to have hearing impairment. In patients with subjective or subclinical hearing deficits, it mainly affected high frequencies. The findings in this cohort suggested a cochlear origin of hearing loss [115]. The onset of the disease is usually before the age of 20 years.

Among the ocular findings, chronic progressive external ophthalmoplegia is the commonest, usually in the form of ptosis, which may be present in up to 89% of cases. In the largest case series to date, pigmentary retinopathy was found in 71% of patients [116]. The retinopathy typically assumes a salt and pepper appearance [117]. Interestingly, bilateral retinoschisis, a macular vitelliform-like lesion and subretinal fluid have all been reported [118-120]. OCT may reveal areas of outer retinal layer atrophy and ellipsoid zone disruption [121], while FAF reveals areas of speckled hypo- and hyperautofluorescence [122]. Full-field ERG shows evidence of generalised cone and rod-system dysfunction [19]. Corneal endothelium involvement can lead to corneal decompensation and oedema [123-126].

Maternally inherited diabetes and deafness (MIDD)

MIDD is a mitochondrial disorder caused by disease-causing variants in *MTTL1* (OMIM #590050), most frequently at position 3243A>G [127]. The onset of sensorineural hearing loss and diabetes is in adulthood and additional features seen in other mitochondrial disorders may be present, such as retinopathy, cardiomyopathy, renal abnormalities and neuropsychiatric symptoms [128-131]. In a large multicentric study (n=54) in individuals with the mtDNA 3243G>A variant, sensorineural hearing loss was present in almost all patients, while 43% of patients had myopathy, 15% had cardiomyopathy and 18% had neuropsychiatric symptoms [129]. The age at the diagnosis of deafness was 34.6 ± 13.9 years (range= 2-61). Macular pattern dystrophy was common in this cohort, and present in 86% of patients.

In 2013, a cross-sectional study (n=29) using a multimodal approach, identified retinal features in affected individuals [132]. The fundus appearance varied

from yellowish fleck-like deposits in early stages, which eventually advanced to circumferential areas of chorioretinal atrophy which coalesce over time, while FAF ranged from the presence of hyperfluorescent flecks, to a diffuse central hypoautofluorescent signal corresponding to areas of chorioretinal atrophy in more advanced stages (Figure 3-E, F). Additionally, the authors proposed a 4-grade classification system based on severity of the retinal findings, OCT, and FAF. More recently, a detailed observational retrospective cases series investigated structural features associated with the disease. The authors identified a sequence of OCT features – from ellipsoid zone loss to subretinal deposits, loss of external limiting membrane and RPE atrophy – that could be used as biomarkers for tracking disease progression. They also demonstrated that, RPE and outer retinal atrophy (RORA) was mostly present in a circular ring area centred on the fovea between 5 and 15 degrees of eccentricity [133].

4. OTHER INHERITED DISORDERS

Stickler syndrome

Stickler syndrome (STL), also known as hereditary arthro-ophthalmopathy is a heterogenous disorder characterised by skeletal, orofacial, ocular and auditory abnormalities [134, 135]. It is most commonly autosomal dominant (AD), although AR inheritance has also been reported. It is grouped into four subtypes (STL1, STL2, STL4 and STL5), the most common being the AD types STL1 and STL2, caused by pathogenic variants in *COL2A1* (OMIM # 120140) and *COL11A1* (OMIM #120280), respectively. Frequently present systemic findings include Pierre Robin sequence, flat midface with midline clefting, hearing loss, osteoarthritis and occasional cardiac

abnormalities [134, 136-138]. Hearing impairment is common and predominantly sensorineural, although a conductive mechanism can also be present, particularly in patients with palatal defects [17].

Ophthalmic features are seen in up to 95% of individuals [139], and include high myopia, cataracts - which have been described as wedge and fleck or quadrantic lamellar cortical lens opacities in more than 40% of cases [140] -, vitreoretinal degeneration and high risk of spontaneous retinal detachment (RD) [138]. The vitreous appearance has been described as a discerning feature between STL1 and STL2, with the former producing a congenital 'membranous' anomaly and the latter a 'beaded' vitreous phenotype [141], although extensive phenotypic heterogeneity has been described [142, 143]. RD can develop in over 70% of cases [139, 144, 145], and is usually the result of a giant retinal tear (**Figure 3-D**). Interestingly, in a recent multicentre analysis of affected patients from Korea, splicing variants were the most frequently associated factor with RD (71%) [146]. Although there is no evidence from randomised clinical trials, retrospective reports have suggested that prophylactic cryotherapy and circumferential laser treatment may substantially reduce the risk of RD in STL1 [144, 147, 148]. Re-detachments are common and often respond well to repeated surgery. In a long-term follow-up of a cohort of 29 eyes of STL patients who underwent RD surgery, success was achieved in 97% of eyes with an average of 2.3 surgeries [149]. Other ocular features include glaucoma in 10% of patients [145].

Norrie disease

Norrie disease is an X-linked recessive condition associated with the gene *NDP* (OMIM #300658) [150, 151]. Variants in *NDP* have also been associated with familial

exudative vitreoretinopathy, persistent hyperplastic primary vitreous (PHPV, also known as persistent foetal vasculature, PFV), retinopathy of prematurity and Coats disease [152]. It is characterised by proliferative changes in the retina and early blindness, developmental delay in approximately half of patients, and hearing loss in about a third of patients [150, 153, 154]. Other features include seizures and peripheral vascular abnormalities [155, 156]. The hearing loss is sensorineural in nature, mild, asymmetric and high frequency in adolescence, progressing to severe loss around 35 years of age [155, 157, 158]. Significant phenotypic heterogeneity may be found, even in members of the same family [159].

Affected patients typically have a transparent lens with congenital posterior synechiae at birth, although the synechiae may develop within a few months of life. In the retrolental space, there is typically a yellowish-white proliferating mass, which can be complicated by anterior synechiae, iris atrophy, cataracts, corneal opacities and RD (**Figure 3-B**) [154]. Microphthalmia may also be present. Phthisis bulbi often develops within the first decade of life [160]. Walsh et al retrospectively reported 14 cases of Norrie disease, all of which underwent vitrectomy with or without lensectomy prior to 1 year of age. Seven maintained at least light perception in one eye, while only 8% of eyes became phthisical; early vitrectomy may thereby be worthy of consideration [161].

CHARGE syndrome

CHARGE is a complex genetic syndrome first described in 1981, with an estimated incidence of 1 per 12,000 [162, 163]. It is caused by heterozygous variants in *CHD7* (OMIM #608892), a member of the chromodomain helicase DNA-binding protein family [164], which has a role as a transcription regulator of both nucleoplasmic and

nucleolar genes [165]. It has also been associated with heterozygous variants in *SEMA3E* (OMIM #608166) [166-168].

It follows a recognisable pattern of congenital anomalies - coloboma, heart disease, choanal atresia, retarded growth and development, genital hypoplasia and ear abnormalities [169, 170]. Bilateral and asymmetric external ear malformations are virtually present in all affected individuals, as well as deafness, which is usually of mixed type [171]. Colobomas with or without microphthalmia may be seen in up to 90% of patients (**Figure 3-C**) [163, 172]. Colobomas are generally bilateral and may affect the retina, choroid and optic disc and, more rarely, the iris [171, 173]. The usual cause for significant decrease in visual acuity is the involvement of the macula in the coloboma. Other contributing features to vision loss include microcornea, nystagmus, severe myopic astigmatism, anisometropia, cataracts and RD [173, 174].

Alport syndrome

Alport syndrome (AS) is a genetically and clinically heterogenous disorder caused by pathogenic variants in *COL4A5* (OMIM #303630), *COL4A3* (OMIM #120070) and *COL4A4* (OMIM #120131), and can be inherited in X-linked, AR (with digenic inheritance reported in *COL4A3* and *COL4A4*) and rarely in AD fashion [175-178]. These genes encode alpha chains of type IV collagen, the most common protein found in basement membranes [179]. Affected patients typically develop glomerulonephropathy and subsequent renal failure, with varying degrees of sensorineural hearing loss and a plethora of ocular findings - which include corneal opacities, anterior lenticonus, earlier-onset cataracts and flecked retinopathy [175, 180]. Due to the severity of the renal impairment, early recognition of the syndrome is essential as angiotensin-converting enzyme inhibitors and angiotensin receptor

blockers have been shown to be safe and efficient in reducing proteinuria, delaying renal failure and improving life expectancy [181-184].

Other reported retinal findings include a dull macular reflex, bull's eye maculopathy, temporal macular thinning, foveal hypoplasia and the formation of macular holes [185-188]. FAF may reveal a pattern of splotchy AF in the mid-periphery in the absence of peripheral retinopathy [186]. Recent reports of OCT and OCT-angiography in affected individuals showed a foveal phenotype that ranges from foveal hypoplasia and absence of foveal avascular zone, to an increase in the foveal avascular zone and a 'stair-case' foveal sign [176, 187, 189]. A cross-sectional study investigating the characteristics of the choroid in 33 patients with AS, found that the choriocapillaris flow deficit was higher in individuals with a history of kidney transplant ($p= 0.006$), suggesting a more severe choriocapillaris impairment in patients with severe kidney disease that require transplantation [190]. Due to potential abnormalities in the vitreoretinal interface, macular hole repair surgery may be challenging, but can lead to successful closure and may benefit selected patients [186, 191, 192].

DISCUSSION AND FUTURE DIRECTION

Several inherited disorders have been described that share impairment of both vision and hearing, a condition known as dual-sensory impairment or DSI. Individuals with impairment in one sensory organ tend to use the functioning organ to compensate in their daily functioning; however, having impairment of both sensory organs can have significant, and often synergistic, detrimental effects on patient’s quality of life and physical functioning [193]. This has been shown in older adults where sensory impairment is typically insidious, which may give patients time to adapt. Sensory

impairment in inherited disorders typically onsets shortly after birth and is usually profound in early life, as has been described for most disorders above. This can result in even further detrimental effect of DSI on functioning and quality of life in young patients; however, this has not been studied yet. Studies are needed to better understand the effect of DSI on functioning in inherited disorders. Another important consideration is the need for specialised multi-disciplinary care in most of the conditions mentioned in this manuscript. The diagnosis of these diseases may have important systemic consequences, for which critical further workup may be required. Moreover, although hearing loss and retinal abnormalities are common findings amongst the diseases described herein, these are very distinct conditions. There is usually a constellation of other findings which, when combined, suggest a specific disorder. Hearing loss and pigmentary retinopathy with concomitant lack or decreased skin pigmentation and blonde fundi, for instance, would suggest an auditory-pigmentary syndrome; whereas, maternally inherited traits suggest mitochondrial disorders, and the presence of osteoarthritis, cardiac abnormalities and Pierre-Robin sequence may imply Stickler syndrome. Table 2 summarises the main defining characteristics of each syndrome, which may guide clinicians to help establish the diagnosis, and also perform and interpret molecular testing. In addition to differentiating the clinical phenotypes of the various genetic conditions included in this review, the clinician should be mindful of other non-genetic conditions that can mimic these presentations, such as congenital rubella syndrome, and rule these out before diagnosing a genetic cause of DSI. Despite the broad availability of genetic testing, patients with DSI should be referred to specialist tertiary centers, in conjunction with genetic counselling, for comprehensive clinical evaluation and

interpretation of genetics results, also given the possible systemic implications, which may even be life-threatening.

As our knowledge in genetic medicine increases, new diseases featuring DSI will be identified, and novel genes will be mapped, which will ultimately increase our understanding to better assist patients in which the molecular diagnosis currently remains unclear. An accurate diagnosis at the earliest opportunity and better understanding of disease natural history are key for providing informed advice on prognosis and genetic counselling, as well as for the development of novel therapeutics and improving the quality of life in affected individuals.

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FIGURE LEGENDS

Figure 1: Retinal imaging in Usher syndrome (USH)

(Rows A-C) Retinal imaging (pseudocolour fundus imaging, fundus autofluorescence and optical coherence tomography) of three patients with USH in the same age group. (A) Retinal imaging of a 25-year-old patient heterozygous for c.5260C>T; p.(Gln1754*) and c.5101C>T; p.(Arg1701*) in *MYO7A*. There is diffuse RPE mottling, a perimacular ring of hyperautofluorescence and outer retinal atrophy, with a relatively preserved central retina. (B) A 26-year-old patient homozygous for the c.2299delG; p.(Glu767Serfs*21) variant in *USH2A*. There is diffuse RPE mottling, outer retinal atrophy with preserved central retinal lamination. Interestingly, the FAF reveals a radial pattern of hypoautofluorescence in the nasal retina and following the vascular arcades. (C) A 21-year-old patient heterozygous for c.118T>G; p.(Cys40Gly) and c.149_152delinsTGTCCAAT; p.(Ser50Leufs*12) in *CLRN1*. There are patchy areas of hypoautofluorescence surrounding the vascular arcades to the mid-periphery and a perimacular ring of increased signal. OCT reveals outer retinal atrophy, central preservation of the ellipsoid zone which is otherwise disrupted and tiny intraretinal cystic spaces.

Figure 2: Retinal imaging in Bardet-Biedl syndrome (BBS)

(Rows A-C) Pseudocolour fundus imaging, fundus autofluorescence (FAF) and optical coherence tomography (OCT) of three patients, illustrating the range of retinal features in BBS. (A) Retinal imaging of a 28-year-old patient homozygous for the c.1169T>G; p.(Met390Arg) variant in *BBS1*. Fundus reveals diffuse RPE mottling with involvement of the posterior pole and pigment deposition in the mid-periphery.

FAF reveals a perimacular hyperautofluorescent ring circumscribed by regions of hypoautofluorescence, and OCT shows disorganization of retinal architecture, with diffuse ellipsoid zone disruption and RPE atrophy. (B) Imaging of a 36-year-old patient heterozygous for the variants c.226C>T; p.(Leu76Phe) and c.271dup; p.(Cys91Leufs*5) in *BBS10*. The retinal phenotype is milder and more restricted to the central retina as shown on FAF and OCT. (C) A 20-year-old patient with a cone-rod dystrophy phenotype due to pathogenic variants in *BBS12* - c.714dup and c.1643dup; p.(Glu549Glyfs*9). There is relatively preserved retinal architecture, with central ellipsoid zone disruption and a perimacular hyperautofluorescent ring, with some hypoautofluorescent areas near the vascular arcades.

Figure 3: Widefield imaging in patients with selected syndromes

(A) Pseudocolour imaging of an individual homozygous for c.2964_2965; p.(Thr989Leufs*6) in *ALMS1*. Severe RPE mottling, vessel attenuation and optic disc pallor can be seen. (B) Pseudocolour of a male patient with a pathogenic variant in *NDP*, namely c.335G>A; p.(Gly112Glu). There are multiple laser marks due to extensive sessions of cryotherapy and photocoagulation after bilateral exudative retinal detachments. (C) Pseudocolour imaging in a patient with the heterozygous *CHD7* variant c.1339C>T; p.(Gln447*). A large inferonasal chorioretinal coloboma involving the optic disc and the macula can be seen. This patient also had malformed ears, nystagmus and left facial nerve palsy. (D) Large inferior retinal detachment in an individual with Stickler syndrome due to a heterozygous intronic variant in *COL2A1*, c.1996-9G>A. This variant is predicted to create a de novo acceptor site which results in mis-splicing. This patient also had a cleft lip. (E, F) Widefield fundus photo and corresponding FAF of an individual with Maternally

Inherited Diabetes and Deafness (MIDD), with the common variant m.3243A>G (10% heteroplasmy). The fundus reveals central RPE atrophy surrounded by yellowish pattern-like flecks, which are more clearly visible in the FAF as hyperautofluorescent speckles.

Table 1: Table summarising the phenotype, the approved HUGO Gene Nomenclature Committee (HGNC), chromosomal (Chr) location and gene-specific function/classification. N/A: not applicable; mtDNA: mitochondrial DNA.

Phenotype	HGNC	Chr location	Function/Classification
Bardet-Biedl syndrome			
BBS1	*BBS1*	11q13.2	BBSome
BBS2	*BBS2*	16q13	BBSome
BBS3	*ARL6*	3q11.2	BBSome-associated GTPase that participates in its assembly
BBS4	*BBS4*	15q24.1	BBSome
BBS5	*BBS5*	2q31.1	BBSome
BBS6	*MKKS*	20p12.2	Chaperonin/BBSome
BBS7	*BBS7*	4q27	BBSome
BBS8	*TTC8*	14q31.3	BBSome
BBS9	*PTHB1*	7p14.3	BBSome
BBS10	*BBS10*	12q21.2	Chaperonin
BBS11	*TRIM32*	9q33.1	E3 ubiquitin ligase
BBS12	*BBS12*	4q27	Chaperonin
BBS13	*MKS1*	17q22	B9 domain-containing protein that associates with basal bodies and primary cilia
BBS14	*CEP290*	12q21.32	Centrosomal protein involved in ciliary assembly/trafficking
BBS15	*WDPCP*	2p15	Localizes to the base of cilia and controls planar cell polarity, ciliogenesis and cell migration
BBS16	*SDCCAG8*	1q43-q44	Centrosomal protein involved in ciliogenesis regulation
BBS17	*LZTFL1*	3q21.31	BBsome-associated protein involved in signalling of *SHH*
BBS18	*BBIP1*	10q25.2	BBSome
BBS19	*IFT27*	22q12.3	G protein involved in intraflagellar transport and cell division
BBS20	*IFT172*	2p23.3	Protein involved in intraflagellar transport
BBS21	*CFAP418*	8q22.1	Localised to the base of the photoreceptor connecting cilium and likely involved in primary cilia function

BBS22	*IFT74*	9p21.2	Component of IFT complex B, which is required for ciliogenesis
Usher syndrome			
USH1B	*MYO7A*	11q13.5	Unconventional myosin that enables cargo transportation
USH1C	*USH1C*	11p15.1	Harmonin involved in anchoring/scaffolding
USH1D	*CDH23*	10q22.1	Cadherin involved in maintenance/organisation of cilia
USH1E	*Unknown*	21q21	Unknown
USH1F	*PCDH15*	10q21.1	Calcium-dependent cell-adhesion cadherin
USH1G	*USH1G*	17q25.1	Anchoring/scaffolding protein
USH1H	*Unknown*	15q22-q23	Unknown
USH1K	*Unknown*	10p11.21-q21.1	Unknown
USH2A	*USH2A*	1q41	Involved in maintenance of periciliary membrane complex/regulation of intracellular protein transport
USH2C	*ADGRV1*	5q14.3	G-protein coupled receptor required for maintenance of the periciliary membrane complex
USH2D	*WHRN*	9q32	Required for periciliary membrane complex maintenance/involved in formation of scaffolding protein complexes
USH3A	*CLRN1*	3q25.1	Presumable role in analogous synapses within the retina
USH4	*ARSG*	17q24.2	Lysosomal enzyme active in the degradation of heparan sulfate
Stickler syndrome			
STL1	*COL2A1*	12q13.11	Type II collagen
STL2	*COL11A1*	1p21.1	Role in fibrillogenesis
STL4	*COL9A1*	6q13	Structural component of the vitreous and hyaline cartilage
STL5	*COL9A2*	1p34.2	Structural component of the vitreous and hyaline cartilage
Alstrom disease	*ALMS1*	2p13.1	Involved in centriole structure and function

Tietz albinism-deafness syndrome	*MITF*	3p13	Transcription factor
Waardenburg syndrome			
WS1	*PAX3*	2q36.1	Transcription factor
WS2A	*MITF*	3p13	Transcription factor
WS2D	*SNAI2*	8q11.21	Transcriptional repressor that modulates basal transcription
WS2E	*SOX10*	22q13.1	Transcription factor
WS3	*PAX3*	2q36.1	Transcription factor
WS4A	*EDNRB*	13q22.3	Nonselective endothelin receptor type B
WS4B	*EDN3*	20q13.32	Endothelin 3
WS4C	*SOX10*	22q13.1	Transcription factor
Norrie disease	*NDP*	Xp11.3	Plays a central role in retinal vascularisation
CHARGE syndrome	*CHD7*	8q12.2	Transcription regulator
Alport syndrome			
ATS1	*COL4A5*	Xq22.3	Component of glomerular basement membranes
ATS2	*COL4A3 and COL4A4*	2q36.3	Component of glomerular basement membranes
ATS3	*COL4A4*	2q36.3	Component of glomerular basement membranes
Mitochondrial disorders			
Kearns-sayre syndrome	Various mtDNA deletions	mtDNA	Mitochondrial DNA has a role in regulation of cellular metabolism, apoptosis and oxidative stress control
Maternally inherited diabetes and deafness (MIDD)	mtDNA mutation (commonly m.3243G>A)	mtDNA	Mitochondrial DNA has a role in regulation of cellular metabolism, apoptosis and oxidative stress control

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Table 2: Table summarising the main ocular findings, hearing loss characteristics and other defining systemic features that differentiate the diseases. EZ: ellipsoid zone; RPE: retinal pigmented epithelium HL: hearing loss

CONDITION	OCULAR FINDINGS	HEARING LOSS	OTHER SYSTEMIC FEATURES
USHER SYNDROME	Typical rod-cone dystrophy	Sensorineural HL with varying age of onset according to the subtype	Balance problems in USH1 due to vestibular dysfunction
BARDET-BIEDL SYNDROME	Phenotypic heterogeneity varying from generalised rod-cone to cone-rod dysfunction, often with early macular involvement	Usually conductive HL secondary to otitis, but sensorineural HL can be associated	Renal dysfunction, obesity, hypogonadism, postaxial polydactyly and cognitive impairment
ALSTROM SYNDROME	Severe pan-retinal degeneration; nystagmus and photophobia, with or without nyctalopia, with an age of onset of 6 to 9 months old; visual prognosis is poor	Progressive sensorineural HL often in the 1st decade of life; conductive component can be present due to chronic and acute otitis media	Child obesity, diabetes mellitus, urological dysfunction, dilated cardiomyopathy, systemic fibrosis, and renal, pulmonary and hepatic failure
TIETZ ALBINISM DEAFNESS SYNDROME	Affected individuals have blue eyes and a diffuse lack of retinal pigmentation; there are no other ocular abnormalities such as nystagmus, photophobia or other findings as seen in conditions with blonde fundi	HL is bilateral, sensorineural, congenital and profound, with speech rarely developing	Individuals are born "snow white", and gradually gain pigmentation; adults have fair skin, blonde to white hair and white eyelashes/eyebrows
WAARDENBURG SYNDROME	Iris pigmentation varies from brown, to sectoral hypopigmentation, to the classical heterochromia irides; fundus often reveals pigmentary changes ranging from a blonde fundus, to blonde areas adjacent to patchy hyperpigmented areas; dystopia canthorum is frequent	Bilateral HF, with variable intra- and interfamilial expression; occurs in about 25% of patients with WS1 and 50% of WS2 individuals	Variable systemic features, but pigmentary abnormalities of the hair, such the characteristic white forelock, are common features; some subtypes display musculoskeletal abnormalities of upper limbs and Hirschsprung disease of the colon (WS3 and WS4, respectively)
KEARNS-SAYRE SYNDROME	Chronic progressive external ophthalmoplegia, particularly in the form of ptosis, is frequent; retinopathy usually has a salt and pepper appearance; retinoschisis and a macular vitelliform-like lesion have been reported; corneal involvement can lead to decompensation	Bilateral sensorineural HL with possible cochlear origin; individuals with subjective/subclinical HL are mainly affected in high frequencies	Other features include heart block, cerebellar ataxia, endocrine disorders, cognitive impairment, and increased levels of cerebrospinal fluid

MATERNALLY INHERITED DIABETES AND DEAFNESS	Characteristic pattern-like dystrophy that ranges from early yellowish flecked deposits to chorioretinal atrophy in later stages	Sensorineural HL present in virtually all patients	Other features include cardiomyopathy, renal abnormalities and neuropsychiatric symptoms
STICKLER SYNDROME	Membranous or beaded vitreous phenotype; cataracts and vitreoretinal degeneration can develop, whereas retinal detachments are common	HL is common and predominantly sensorineural, although a conductive or mixed mechanism can be present, in patients with palatal defects	Pierre-Robin sequence, flat midface with midline clefting, cardiac and musculoskeletal abnormalities
NORRIE DISEASE	Transparent lens with congenital posterior synechiae at birth or within a few months of life; yellowish-white proliferating retrolental mass, which can complicate with anterior synechiae, cataracts, corneal opacities and retinal detachment; microphthalmia may be present, and phthisis bulbi often develops within the 1st decade of life	HL is sensorineural, mild, asymmetric and high frequency in adolescence, progressing to severe loss around the 3rd decade of life	Seizures, developmental delay, and peripheral vascular abnormalities
CHARGE SYNDROME	Bilateral colobomas with or without microphthalmia are very frequent; colobomas may affect retina, choroid, optic disc and iris, with a poor visual prognosis if involvement of macula; microcornea, nystagmus, cataracts and retinal detachments can be present	Bilateral and asymmetric external ear malformations are present in virtually all patients; HL is of mixed type	Choanal atresia, retarded growth/development, heart disease, genital hypoplasia and ear abnormalities
ALPORT SYNDROME	Flecked retinopathy, corneal opacities, anterior lenticonus and earlier-onset cataracts may be present; other reported features include foveal hypoplasia, bull's eye maculopathy and formation of macular holes	Varying degrees of sensorineural HL	Severe glomerulonephropathy that typically evolves to renal failure