

# Genodermatoses with hearing impairment



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Hearing loss is a prominent feature in multiple genodermatoses. Underappreciation of auditory deficits can misdirect proper diagnosis by the treating dermatologist. This review reviews the anatomic, developmental, and embryologic aspects that characterize the ear and summarizes genodermatoses that have aberrant auditory findings. The latter are classified into neural crest, metabolic, pigmentary, craniofacial, and a miscellaneous category of disorders lacking specific cutaneous findings. The algorithms provided in this review enable treating dermatologists to better recognize and manage genodermatoses with ear involvement. (*J Am Acad Dermatol* 2021;85:931-44.)

**Key words:** cutaneous manifestations; deafness; genodermatoses; inherited skin disorders; syndromic hearing loss.

## INTRODUCTION

Hearing impairment is the leading cause of childhood disability and is one of the most common birth defects.<sup>1</sup> In 30% of affected patients, congenital deafness will be a part of a broader syndrome requiring vigilant screening and early intervention. The adoption of universal newborn hearing screening has led to better outcomes, but additional clinical clues can be helpful in identifying an underlying constellation of associated findings in syndromic cases.<sup>1</sup>

In the field of dermatology, many genodermatoses can develop hearing loss (sensorineural, conductive, or mixed). The aim of this review is to familiarize physicians with the clinical characteristics of these disorders (Tables I and II),<sup>2-49</sup> alerting them to the possibility of hearing deficits. A diagnostic algorithm (Figs 1-3) is provided to ensure early diagnosis, intervention, and rehabilitation.

## EAR ANATOMY

The ear can be anatomically divided into 3 portions, from the outside of the skull to the inside. The most exterior section is the outer ear, which

comprises the pinna and the external auditory canal. The tympanic membrane separates the outer ear from the middle ear.<sup>51</sup> The middle ear consists of 3 bony extensions (malleus, incus, and stapes) in the tympanic cavity, covered by the temporal bone. The tympanic cavity connects with the nasopharynx through the eustachian tube, which is necessary for pressure to equalize in the middle ear and for the proper transfer of sound waves. The eustachian tube is lined with respiratory epithelium and mucosa, similar to the nose and throat.<sup>51</sup>

After sound amplification in the middle ear, sound waves reach the inner ear, consisting of 3 major organs: cochlea, vestibule, and the semicircular canals. The cochlea is spiral shaped and makes 2.75 turns around its axis. Sound waves are transduced into electric stimuli in the cochlea. Its unique shape allows for the differentiation of sound frequencies. The cochlear duct is an endolymph-filled cavity that transduces vibrations into electric impulses carried through the vestibulocochlear nerve to the brain, playing an essential role in converting sound waves into audible sounds. The semicircular canals are specifically stimulated by rotational

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movement (angular acceleration) and the vestibule responds to changes in position vertically (with respect to gravity or linear acceleration). All 3 organs play a crucial role in providing a sense of balance, position, and proprioception.<sup>51</sup>

## EAR EMBRYOLOGY

An appreciation of the gross and molecular embryologic events underlying the development of the ear provides the strong conceptual framework for understanding the loss of hearing that can take place in the genodermatoses under consideration. Although the temporal events and the molecular components implicated in the development of the various structures of the ear overlap, the embryology of each of the 3 major components of the ear (external, middle, and inner) will be discussed separately while highlighting relevant links to cutaneous embryology.

### External ear

Of the 3 anatomic divisions, the embryologic development of the external ear remains the least studied. The first major external ear structure, the pinna, is derived from 6 mounds known as the 6 hillocks of His, which first appear during the sixth week of gestation. These hillocks originate from the first and second pharyngeal arches and their growth and subsequent fusion forms the pinna. After the hillocks fuse, the pinna peels away from the head at 18 weeks of gestation with the completion of its development by the twenty-second week.

In their seminal work on auricle morphogenesis in mice, Minoux et al<sup>52</sup> earmark the homeobox transcription factor *Hoxa2* as the master transcriptional orchestrator of the pinna genetic program. *Hoxa2* was found to act via the bone morphogenetic protein signaling pathway by the direct regulation of bone morphogenetic protein 4 and bone morphogenetic protein 5. An *Hoxa2* target with both dermatologic and otic relevance is *eyes absent 1*.<sup>18</sup> Mutations in *eyes absent 1* are linked to defects in the second branchial arch and manifest dermatologically as branchial cysts or sinuses, which are characteristic features in branchio-otic and branchio-oto-renal syndromes.<sup>18</sup> The associated hearing loss in these syndromes can vary from

mild to profound, stable, or progressive and can even differ between the 2 ears. Other ear abnormalities include preauricular pits or tags, a smaller outer ear, and a narrow outer ear canal. Branchio-otic/branchio-oto-renal patients who develop hearing loss should undergo appropriate rehabilitation measures, including annual or semi-annual audiometries and immediate

management of otitis media. Other interventions could include hearing aids or surgical correction of the associated defects. Semi-annual assessment of the renal function is required in patients with branchio-oto-renal, as these patients might require dialysis, kidney transplant, or other surgical interventions.<sup>18</sup>

The external auditory canal is the second major external ear structure, the development of which relies

on the formation of the “meatal plug” by the ninth week of gestation.<sup>53</sup> As the majority of the meatal plug undergoes a gradual process of resorption, the innermost surface in contact with the primordial malleus develops into the outer aspect of the primordial tympanic membrane at 15 weeks of gestation.<sup>53</sup>

TCOF1 is a nucleolar protein that regulates ribosomal gene transcription and DNA damage repair in precursors of neural crest cells. It is crucial in the development of the neural crest-derived facial bones, the pinna, and the external auditory canal as corroborated by findings of cleft palate, hypoplasia of the facial bones, an atretic auditory canal, and microtia in individuals with Treacher-Collins syndrome (TCS).<sup>19</sup> Newborns with TCS may require special positioning or tracheostomy to manage the airway; hence, assessing the fetal profile with a prenatal ultrasound is advised for appropriate management and is best done after 30 weeks.<sup>54</sup> Downslanting palpebral fissures, micrognathia, and low-set ears can be detected, as can polyhydramnios. Amniocentesis can be done to confirm the diagnosis. These patients might require continuous apnea/oxygen-saturation monitoring and a detailed assessment of airway obstruction. Other than airway management, other major concerns are corneal scarring, adequate feeding, and growth. Parenteral feeding, aspiration precautions, and ophthalmologic interventions should be discussed with the family. Once these measures are implemented, the remaining

## CAPSULE SUMMARY

- Hearing impairment can be an outcome of many genodermatoses and can cause significant morbidity in affected children.
- Because timely diagnosis can assist in early interventions, this study reviews the pertinent genodermatoses, emphasizing the cutaneous manifestations and type of hearing impairment, and provides a diagnostic algorithm that dermatologists can follow.

*Abbreviations used:*

Cx:	connexins
CHARGE:	coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies
KID:	keratitis-ichthyosis-deafness
TCS:	Treacher-Collins syndrome

dysmorphology can be considered, depending on the anatomic structure and the preference of the parents. The management of the hearing deficits can be attempted by bone conduction amplification and speech therapy, among other measures.

The chromatin remodeler CHD7 is another vital component in neural crest cell induction and maintenance. Mutational defect in CHD7 as seen in Coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies (CHARGE) syndrome is associated with a broad array of impairments in several structures derived from the neural crest, including all 3 ear compartments.<sup>54</sup> Diagnosis of CHARGE syndrome relies on the detection of the characteristic 4 Cs: Coloboma, choanal atresia, cranial nerve abnormalities, and the presence of CHARGE ears.<sup>55</sup> The associated sensorineural hearing loss can be mitigated with hearing aids; however, the malformed ear, also characteristically known as the CHARGE ear, might require surgical remodeling to support hearing aid use in light of the architecturally distorted ear cartilage. Cochlear implants have also been used successfully in these patients.<sup>56</sup> Chronic airway problems and aspiration arising from abnormalities in the nasopharyngeal pathway might also prompt the use of tracheostomy while jejunostomy or gastrostomy feeding tubes may be required for the associated feeding difficulties.<sup>57</sup> A pediatric anesthesiologist should be consulted preoperatively to decide on the optimal intraoperative ventilation mechanism and to preside over intubation efforts, which frequently fail. Cardiology consultation should be sought in infants with suspected CHARGE syndrome, as the possible presence of a patent ductus arteriosus would require prostaglandin therapy to promote ductal patency.

### **Middle ear**

The embryologic and molecular events governing development of the middle ear are better elucidated than those pertaining to the external ear. The 3 ossicles (malleus, incus, and stapes) owe the bulk of their development to the neural crest cells derived from the first and second pharyngeal arch, except for

the minor mesodermal contribution limited to the part of the footplate surface in contact with the oval window. The 2 other major components of the middle ear, the eustachian tube and the middle ear cavity, are derived from the proximal and distal part of the tubotympanic recess, respectively. The formation of the tubotympanic tube comes about by the invagination of the first pharyngeal pouch toward the developing middle and inner ear structures. Subsequent rupture of the distal end of this recess floods the area contiguous to the immature cartilaginous ossicles with neural crest-derived mesenchyme. Eventually, the neural crest cells in question undergo cavitation, in which these cells regress in a ventral-to-dorsal direction to leave the ossicles stranded in an air-filled cavity, the middle ear cavity. The entirety of this cavity is encapsulated within the bony auditory bulla, another neural crest-derived structure. Failure to complete the cavitation process is an additional observation noted in TCS patients with TCOF1 mutations. The partially filled air cavity and the subsequent diminution of the auditory bulla preclude the proper vibration of the ossicles and contribute to the conductive hearing loss found in TCS.<sup>58</sup>

Rigueur et al<sup>50</sup> recently described a fundamental role for Fgfr2 in the development of all major bony middle ear structures. Distortion and size reduction of auditory bullae secondary to incomplete cavitation as well as ectopic bone formation on the ossicles contributed to the conductive hearing loss observed in Fgfr2 cKO mice. This confirms the role of Fgfr2 in the proper skeletal maturation of middle ear structures and provides a theoretical basis for the conductive hearing loss seen in Fgfr2-mutated disorders, such as Apert syndrome.<sup>20</sup> In the skin, Fgfr2b is present on keratinocytes, hair follicles, and sebaceous glands and induces keratinocyte proliferation and differentiation when bound by FGF,<sup>59</sup> while sebaceous gland activation via Fgfr2b is implicated in acne pathogenesis, a staple of Apert syndrome.

As the most severe of the FGFR2-related craniosynostosis syndromes, Apert syndrome presents with the triad of midfacial hypoplasia, symmetric syndactyly of the limbs, and craniosynostosis. As this syndrome is autosomal dominant, diagnosis can be made definitively if the typical physical examination findings occur in the setting of a positive family history for this disease. The mutation can also arise spontaneously and subsequent detection might require the use of imaging modalities, such as computed tomography, ultrasound, or magnetic resonance imaging, as well as prenatal genetic testing. Early surgical correction of the craniosynostosis is necessary to reduce the associated sequelae,

**Table I.** Genodermatoses with hearing loss

Disease	Gene	Mode of inheritance	Clinical findings	Reference
Diseases of gap-junction channel defects				
Vohwinkel syndrome (classic type)	GJB2	AD	SNHL, diffuse honeycomb-like PPK, pseudoainhum, starfish-shaped keratoses of joints (linear keratotic plaques of knees, scarring alopecia)	14
Keratitis-ichthyosis-deafness syndrome	GJB2	AD	SNHL, ichthyosis, keratitis, photophobia, corneal vascularization, hyperkeratosis of the palms and soles, erythrokeratoderma, follicular hyperkeratosis, and recurrent bacterial and fungal infections	15
PPK with deafness	GJB2 MTTS1 (mitochondrial)	AD	Progressive SNHL, PPK	16
Bart Pumphrey syndrome	GJB2	AD	SNHL, PPK, knuckle pads, leukonychia	17
Hystrix-like ichthyosis deafness syndrome	GJB2	AD	SNHL, mild keratitis, hystrix-like ichthyosis	50
Neural crest-associated diseases				
Waardenburg syndrome	Type 1 & 3: PAX3 Type 2: MITF, SNAI2 Type 4: SOX10, EDNBR, EDN3	AD (type 4 can be AR)	It is the most common form of inheritable congenital deafness (SNHL); 60% in WS1 and 90% in WS2 Pigmentation abnormalities that can occur in the eyes (heterochromia iridis), hair, skin (white forelock and premature hair graying), and the cochlear stria vascularis	2
Piebaldism	KIT SNAI2	AD	SNHL occurs rarely, poliosis, leukotrichia of eyebrows and eyelashes, congenital well demarcated, symmetric, nonpigmented patches involving the skin of the face, trunk, arms and legs, heterochromia irides, neurologic impairment	3
Tietz syndrome	MITF	AD	Severe congenital bilateral SNHL, generalized uniform hypopigmentation of the skin, may have reddish freckles, blonde to white hair, blue eyes and hypopigmented fundi	3
Oculocutaneous albinism	Type 1: TYR Type 2: OCA2 Type 3: TYRP1 Type 4: SLC45A2 Type 6: SLC24A2 Type 7: C10ORF11	AR	Congenital SNHL has been reported, increased risk of precancerous skin lesions and skin tumors, generalized congenital hypopigmentation of the skin, blonde hair, nystagmus, reduced iris and retinal pigmentation, foveal hypoplasia with reduction in visual acuity, strabismus	3
Metabolic diseases				
Hunter syndrome	Iduronate sulfatase (IDS)	XLR	Conductive hearing loss; firm, flesh-colored to white papules coalescing over scapula; facial dysmorphism; hepatosplenomegaly; joint Contractures; skeletal deformities; upper airway obstruction; valvular heart disease; neurologic deficits.	4

Continued

**Table I.** Cont'd

Disease	Gene	Mode of inheritance	Clinical findings	Reference
Biotinidase deficiency	BTD	AR	SNHL, alopecia, periorificial dermatitis, developmental delay, seizures.	5
Fabry disease	(GLA) $\alpha$ -Galactosidase A	XLR	SNHL, multiple angiokeratomas, extremity pain/paresthesia, whorl-like corneal and lenticular opacities, birefringent lipid globules in urine ("Maltese crosses"), MI, CVA.	6
Alpha-Mannosidosis	?	AR	SNHL, progressive intellectual disability, hearing loss, skeletal anomalies, and coarse facial features	7
$\beta$ -Mannosidosis	$\beta$ -mannosidase (MANBA)	AR	SNHL, MR, speech impairment, aggressive behavior, emotional instability, angiokeratoma, recurrent respiratory infections, epileptic encephalopathy.	8
Kanzaki disease	alpha-N-galactosaminidase (NAGA)	AR	SNHL, angiokeratoma corporis diffusum, mild MR	9
Refsum disease	PHYH PEX7	AR	SNHL, anosmia, early-onset retinitis pigmentosa, variable combinations of peripheral neuropathy, cerebellar ataxia, ichthyosis.	10
Chanarin-Dorfman syndrome	ABHD5	AR	Mixed-type hearing loss, ichthyosis, hepatomegaly, splenomegaly, cirrhosis, cataract, keratopathy, myopathy, MR	11
Rud syndrome	?	?	SNHL, ichthyosis, epilepsy, dwarfism, sexual infantilism, polyneuritis, and macrocytic anemia Overlap with Sjögren-Larsson syndrome	12

AD, Autosomal dominant; AR, autosomal recessive; CVA, cerebrovascular accident; DMII, Type 2 diabetes mellitus; PPK, palmoplantar keratoderma; ?, unknown; MI, myocardial infarction; MR, mental retardation; SNHL, sensorineural hearing loss; WS1, Waardenburg syndrome type 1; WS2, Waardenburg syndrome type 2; XLR, X-linked recessive.

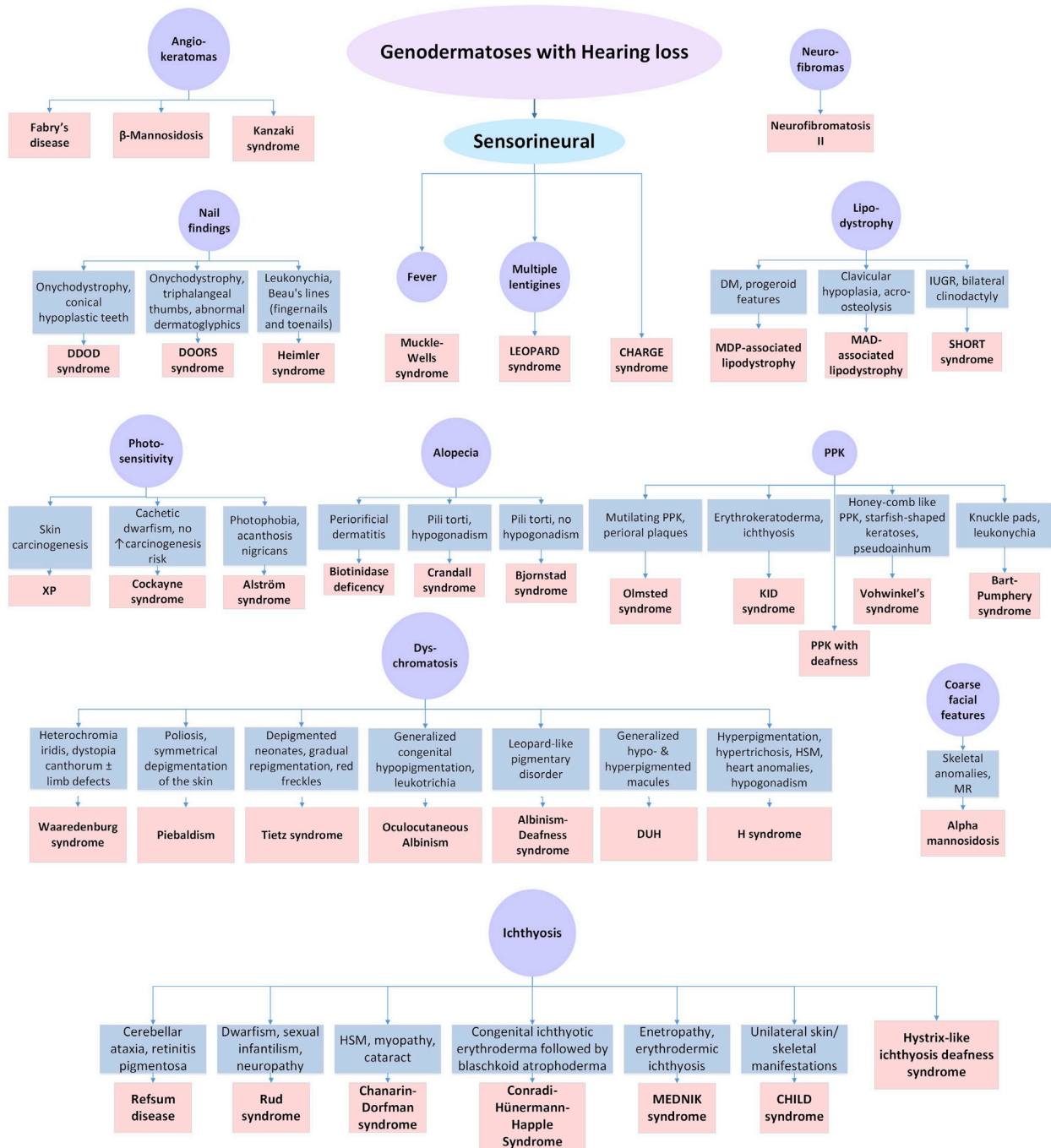
such as vision loss, sleep apnea, and elevated intracranial pressure, yet the benefit of earlier correction is anecdotal and not evidence based. Additionally, patients with Apert syndrome can present with hearing loss, strabismus, acne, and mild-to-moderate intellectual disability. The conductive hearing loss found in Apert syndrome affects up to 80% of patients and can be ameliorated with hearing aids,<sup>60,61</sup> while the refractory moderate-to-severe acne experienced by patients with Apert syndrome has been found to respond to isotretinoin.<sup>62</sup>

### Inner ear

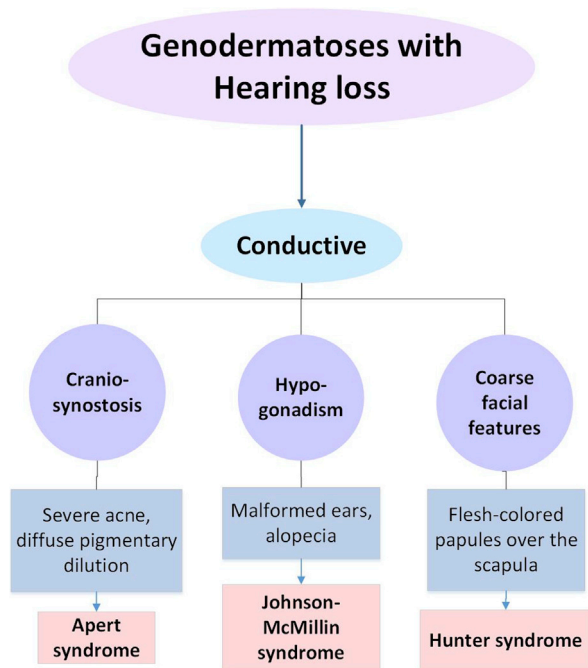
Vis-à-vis the presence of the organ of Corti and the vestibular organs, the inner ear embodies the functional hub of the vestibulocochlear system with valuable insights gleaned from a critical study of its development. The ectodermal otic placode

emerging in the sixth week of gestation is credited with the formation of the membranous labyrinth and the vestibulocochlear neurons. Invagination and subsequent separation of the otic placode yields the otic vesicle. This vesicle gives rise to the non-sensory semicircular and cochlear epithelia and prosensory epithelium, the source of vestibulocochlear ganglion neuroblasts. Neural crest cells eventually migrate and form corridors en route toward the nascent otic vesicle.

Via a complex molecular interplay that has yet to be elucidated, the neural crest cells differentiate into Schwann cells while the prosensory epithelium ultimately develops into the organ of Corti and the 5 vestibular sensory patches, precursors of the 3 cristae and the utricle and saccule. Of immense importance in otic functioning is the stria vascularis, a capillary-rich endolymph-secreting tissue present on the



**Fig 1.** Clinical diagnostic approach to gendodermatoses with sensorineural hearing loss. *CHARGE*, Coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies; *CHILD*, Congenital hemidysplasia with ichthyosiform erythroderma and limb defects; *DOORS* syndrome, Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures syndrome; *DDOD* syndrome, Deafness, congenital, with onychodystrophy; *DM*, Diabetes mellitus; *DUH*, Dyschromatosis universalis hereditaria; *HSM*, hepatosplenomegaly; *PPK*, Palmoplantar keratoderma; *MDP*, Mandibular hypoplasia, deafness, progeroid features; *MEDNIK* syndrome, MR, enteropathy, SNHL, peripheral neuropathy, lamellar and erythrodermic ichthyosis, and keratoderma; *MR*, mental retardation; *SHORT* syndrome, Short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Reiger anomaly and teething delay syndrome; *XP*, Xeroderma pigmentosum; *SNHL*, sensorineural hearing loss.



**Fig 2.** Clinical diagnostic approach to genodermatoses with conductive hearing loss.

lateral wall of the cochlear duct. Proper functioning of the stria vascularis relies on the presence of melanocytic intermediate cells, derived from the neural crest, which fine tune the ionic composition of the potassium-rich endolymph.

Due to the notorious difficulty in conducting genetic studies on intermediate cells, the development of intermediate cells is extrapolated from studies involving the formation of skin melanocytes. The differentiation of melanocytes relies on several molecular interactions that involve *Sox10*, *Pax3*, and *Mitf*, all incriminated in the various types of Waardenburg.<sup>13</sup> Interestingly, the synergistic actions of both *Sox10* and *Pax3* activate *Mitf*, the “master regulator” of the melanocyte differentiation program. Consequently, *Sox10* works with *Mitf* to promote expression of the genes required for melanocyte identity, including *Tyr* and *Tyrp1*.<sup>63,64</sup> Defects in the aforementioned molecular players have profound implications on melanocytic differentiation in the skin and ear with resultant clinical sequelae of leukoderma and sensorineural deafness, respectively. These manifestations are instrumental in the diagnosis of Waardenburg syndrome, which can be made based on the presence of characteristic features. The full complement of clinical features may not manifest in every case, requiring genetic testing for confirmation. The hearing loss experienced by patients with Waardenburg syndrome is sensorineural in nature and requires management with hearing aids or, more definitively, with cochlear

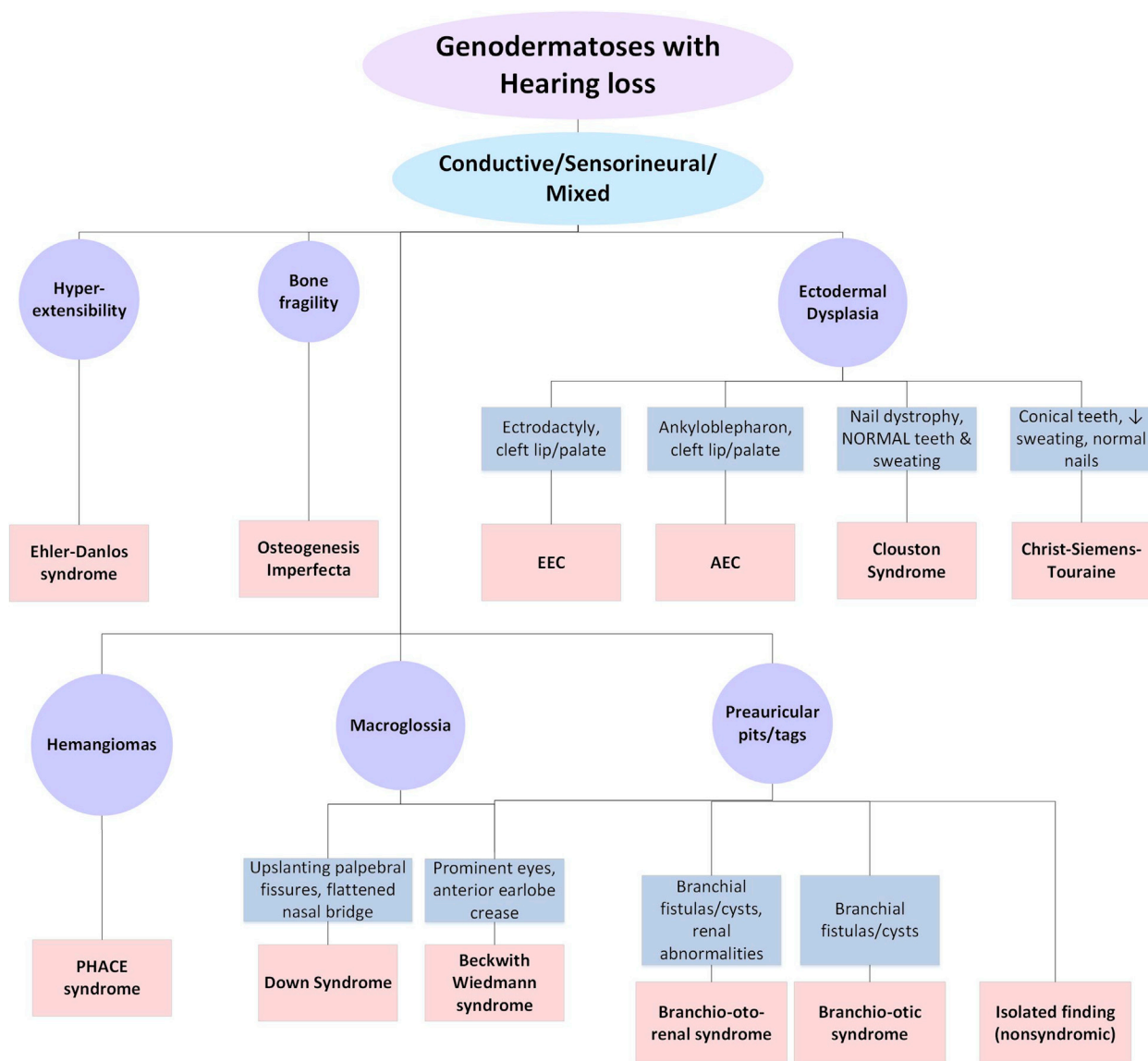
implants. Sun protection is of paramount importance because the depigmented patches are highly susceptible to the damaging effects of ultraviolet radiation. Moreover, certain types of Waardenburg may manifest with skeletal abnormalities (type 3) or associated Hirschsprung disease (type 4) and would necessitate pediatric orthopedic and gastrointestinal consultations, respectively.

Another class of developmentally and functionally pivotal components of the inner ear and the skin are the gap-junction proteins connexins 26 (Cx26) and Cx30. Cx26 and Cx30 are required for proper recirculation of potassium by the intermediate cells; the loss of the latter function underlies the sensorineural hearing loss seen in multiple Cx26-related disorders.<sup>19,53-55</sup> However, a recent paper discovered a developmental role for Cx26 and Cx30: the promotion of intracellular calcium signaling at critical times by the connexins under consideration plays an important role in the development of the inner ear sensory epithelia.<sup>65</sup> With respect to the skin, a tentative role for the connexins was suggested by transfer-dye experiments in which dye transfer revealed keratinocyte organization into “communication compartments” consisting of 20-25 cells.<sup>66</sup> These communication compartments were equated to proliferative units that possibly communicate via connexin channels.<sup>66</sup>

This provides the rationale for the clinical spectrum of aberrant epidermal cornification that characterizes several ectodermal dysplasias where mutations in connexins 26 and 30 are implicated. A mutation in connexin 26 forms the pathogenetic basis for a wide array of syndromes, including Vohwinkel syndrome, Bart Pumphrey syndrome, keratitis-ichthyosis-deafness (KID) syndrome, and palmoplantar keratosis with deafness. Common among all of the aforementioned is the presence of sensorineural deafness that is amenable to cochlear implantation and the presence of diffuse palmoplantar keratoderma that frequently responds to oral retinoids.

In terms of specific clinical features, Vohwinkel syndrome manifests with stellate keratoses on the knuckles and linear keratoses on the knees and elbows. Characteristically, autoamputation of digits can be seen due to the presence of fibrous constriction bands that encircle the digits and toes, also known as pseudoainhum; these cases require surgical release but also have been known to respond to oral retinoids.<sup>67</sup>

On the differential diagnosis of Vohwinkel syndrome is Bart Pumphrey syndrome, another connexin 26-related genodermatosis. Unlike Vohwinkel syndrome, Bart Pumphrey demonstrates



**Fig 3.** Clinical diagnostic approach to genodermatoses with sensorineural, conductive, or mixed hearing loss. *AEC*, Ankyloblepharon, ectodermal defects, cleft lip/palate; *EEC*, Ectrodactyly, ectodermal dysplasia, cleft lip/palate.

leukonychia and knuckle pads, pathognomonic features especially in the context of palmoplantar keratoderma and the deafness. Moreover, Bart Pumphrey syndrome lacks the characteristic stellate keratoses of Vohwinkel syndrome and displays non-mutilating palmoplantar keratoderma.

KID syndrome demonstrates generalized mild hyperkeratosis along with follicular plugging as well as erythron-keratodermic plaques that favor the face and extremities. A staple feature of KID syndrome is the progressive bilateral vascularized keratitis that results in blindness if left untreated; as such, ophthalmology referral should be pursued. Regular dermatologic follow up is also recommended, as patients with KID syndrome have shown an

increased risk of bacterial and fungal infections as well as squamous cell carcinomas.

Hydrotic ectodermal dysplasia, also known as Clouston syndrome, arises due to a mutation in connexin 30 and is typified by the clinical triad of alopecia, palmoplantar keratoderma, and nail dystrophy. In rare cases, patients may exhibit sensorineural hearing loss and early-onset cataracts.

**CONCLUSION**

The ear and the skin are 2 major organ systems developmentally linked by a shared neural crest component that forms a predominant part of their respective embryologic derivations. Defects in any part of the common embryologic elements at critical

**Table II.** Other genodermatoses of various etiologies associated with hearing loss

Disease	Gene	Mode of inheritance	Clinical findings	Reference
Heimler syndrome 1	Peroxisome biogenesis factor 1 gene (PEX1)	AR	SNHL, leukonychia, Beau's lines (fingernails and toenails), amelogenesis imperfecta (secondary teeth)	17
Congenital hemidysplasia with ichthyosiform erythroderma and limb defects	NSDHL	XLD	SNHL (reports), unilateral ichthyotic erythroderma, ipsilateral alopecia, ipsilateral organ aplasia/agenesis, skeletal defects, amelia, stippled epiphyses with or without cleft palate	21
Conradi-Hünermann-Happle syndrome	EBP	XLD	SNHL (reports), craniofacial features, asymmetric shortening of long bones with epiphyseal stippling, congenital ichthyosiform erythroderma (following Blaschko's lines), cataracts	22
Mandibuloacral Dysplasia (MAD) associated lipodystrophy	LMNA	AR	SNHL (reports), lipodystrophy, growth retardation, craniofacial anomalies with mandibular hypoplasia, skeletal abnormalities with progressive osteolysis of the distal phalanges and clavicles, pigmentary skin changes	23
MDP-associated lipodystrophy syndrome	POLD1	AD	SNHL, prominent loss of subcutaneous fat, characteristic facial appearance, metabolic abnormalities (DM)	23
SHORT syndrome	PIK3R1	AD	SNHL, lipodystrophy, intrauterine growth retardation, delayed speech development, bilateral clinodactyly	24
Albinism-deafness syndrome (Ziprkowski Margolis or Woolf syndrome)	?	XL	SNHL, a severe piebald-like phenotype with extensive areas of hypopigmentation (with or without ocular albinism), sparing the buttocks and genital region. Later, multiple hyperpigmented macules appear, giving the skin a leopard-like appearance, heterochromia irides. Suggested to be an X-linked variant of Waardenburg syndrome	25
Dyschromatosis universalis hereditaria	Variable	Variable	High-frequency deafness (SNHL in rare reports), hyperpigmented and hypopigmented macules in a generalized distribution	26
Histiocytosis-lymphadenopathy plus syndrome	SLC29A3	AR	Faisalabad histiocytosis: Joint deformities, sensorineural hearing loss, subsequent development of generalized lymphadenopathy and eyelid swelling Sinus histiocytosis with massive lymphadenopathy: Familial Rosai-Dorfman disease with overlap with H syndrome H syndrome: SNHL, cutaneous hyperpigmentation and hypertrichosis, hepatosplenomegaly, heart anomalies, hypogonadism	27

Continued

**Table II.** Cont'd

Disease	Gene	Mode of inheritance	Clinical findings	Reference
Neurofibromatosis 2	NF2	AD	SNHL secondary to bilateral vestibular schwannomas, risk for a variety of other tumors (meningiomas, astrocytomas, ependymomas, meningioangiomas, neurofibromas)	28
Cockayne syndrome	ERCC8 (CSA) ERCC6 (CSB)	AR	SNHL, cachectic dwarfism, severe neurologic manifestations (microcephaly and cognitive deficits, pigmentary retinopathy, cataracts, ambulatory and feeding difficulties)	29
Xeroderma pigmentosum	XP (A-G)	AR	Progressive neurologic abnormalities (including SNHL), photosensitivity, photophobia, cutaneous pigmentary changes, skin tumors	30
X-Linked CGH	?	XLD	Deafness, mild facial abnormalities, occasional anomalies of the teeth, hair overgrowth	31
PHACE syndrome	?	?	Conductive, sensorineural and mixed hearing loss; posterior fossa malformations; Hhemangiomas; arterial anomalies; cardiac defects; abnormalities of the eye	32
Preauricular skin tags and ear pits	?	AD?	Increased risk for permanent hearing impairment (conductive, sensorineural, and mixed hearing loss)	33
Down syndrome	Trisomy 21	-	Sensorineural, conductive, or mixed hearing loss; up-slanting palpebral fissures; epicanthic folds; brachycephaly; short neck; alopecia areata; atopic dermatitis; elastosis perforans serpiginosa; protruding tongue among others	34
Turner syndrome	(45, X)	XL	Conductive, sensorineural, and mixed hearing loss; short stature; broad chest; webbed neck; low-set ears; gonadal dysgenesis	35
Crandall syndrome	?	AR	SNHL, alopecia (pili torti), hypogonadism	36
Bjornstad syndrome	BCS1L	AR	SNHL, alopecia (pili torti), no hypogonadism	36
LEOPARD syndrome	PTPN11	AD	Multiple lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, SNHL	37
Muckle-Wells syndrome	Cryopyrin (NLRP3)	AD	SNHL, urticaria, amyloidosis triad; acute attacks of fever, arthralgias, myalgias, abdominal pain, conjunctivitis	38

Continued

**Table II.** Cont'd

Disease	Gene	Mode of inheritance	Clinical findings	Reference
Apert syndrome	Fibroblast growth factor receptor 2 (FGFR2)	AD	Mild-to-moderate conductive hearing loss, chronic middle ear disease, ossicular anomalies, craniosynostosis, digital anomalies (syndactyly, broad thumbs), severe acne, Munro acne nevus, nevus sebaceous, diffuse pigmentary dilution, developmental delay	20
Branchio-oto-renal syndrome 1	EYA1, SIX1 & SIX5	AD	Sensorineural, conductive, or mixed hearing loss; structural defects of the outer, middle, and inner ear; branchial fistulas or cysts; preauricular pits and renal abnormalities	18
Branchio-otic syndrome 1	EYA1	AD	Similar to Branchio-oto-renal syndrome without the renal abnormalities	18
CHARGE syndrome (OMIM 214800)	CHD7	AD	Coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies; abnormal outer ears, ossicular malformations (SNHL), Mondini defect of the cochlea and absent or hypoplastic semicircular canals, growth deficiency, orofacial clefts	54
Beckwith-Wiedemann syndrome	Cyclin-dependent kinase inhibitor 1C (CDKN1C)/p57/Kip2 H19 and LIT1	AD	Sensorineural or conductive hearing loss (very rare) due to stapedial fixation; prominent eyes with infraorbital creases, facial nevus flammeus, midfacial hypoplasia, macroglossia, full lower face with a prominent mandible, anterior earlobe creases and posterior helical pits; prominent or persistent midfacial nevus simplex	39-41
Treacher-Collins syndrome	TCOF1 POLR1C POLR1D	AD AR	Conductive and SNHL, bilateral downslanting palpebral fissures, malar hypoplasia, micrognathia, cleft lip/palate, external ear abnormalities	19
Alström syndrome	ALMS1	AR	SNHL, photoreceptor dystrophy, nystagmus, photophobia, truncal obesity, DMII, dilated cardiomyopathy, acanthosis nigricans, flat feet	42
Ehler-Danlos syndrome	Variable	Variable	Conductive, sensorineural, or mixed hearing loss; kyphoscoliosis; respiratory problems; muscle weakness; joint laxity; glaucoma; retinal detachment	43
Osteogenesis imperfecta	Type I collagen	Variable	Conductive, sensorineural, or mixed hearing loss; fragile bones; blue sclera; hyperelasticity of joints and ligaments	44

Continued

**Table II.** Cont'd

Disease	Gene	Mode of inheritance	Clinical findings	Reference
Ectodermal dysplasias	Variable	Variable	Conductive or SNHL, hypodontia, peg-shaped/conical teeth, sparse to absent hair, nail dystrophy, variably decreased sweating	45
Johnson-McMillin syndrome	Variable	AD	Conductive hearing loss, alopecia, anosmia or hyposmia, malformed ears, microtia, atresia of the external auditory canal, hypogonadotropic hypogonadism	46
Olmsted syndrome	TRPV3 MBTPS2	AD XLR	SNHL (very rare), PPK (mutilating), erythematous hyperkeratotic perioral plaques	47
MEDNIK syndrome	AP1S1	AR	MR, enteropathy, SNHL, peripheral neuropathy, lamellar and erythrodermic ichthyosis, keratoderma	48
DDOD syndrome	ATP6V1B2	AD	SNHL; onychodystrophy; conical, hypoplastic teeth	17
DOORS syndrome	TBC1D24	AR	SNHL, onychodystrophy, osteodystrophy, MR, seizures	49

AD, Autosomal dominant; AR, autosomal recessive; CHL, congenital hearing loss; CGH, congenital generalized hypertrichosis; DOORS syndrome, deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures syndrome; DDOD syndrome, deafness, congenital, with onychodystrophy; DMII, Type 2 diabetes mellitus; EYA1, eyes absent Homolog 1; PPK, palmoplantar keratoderma; ?, unknown; MDP, mandibular hypoplasia, deafness, progeroid features; MI, myocardial infarction; MR, mental retardation; SHORT syndrome, short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Reiger anomaly and teething delay syndrome; SNHL, sensorineural hearing loss; XL, X-linked; XLD, X-linked dominant; XLR, X-linked recessive.

junctions in development manifest in any of the genodermatoses discussed. While the cutaneous presentations are eclectic in severity and morphology, auditory sequelae invariably lead to a single, albeit variably severe, manifestation: hearing loss. Despite functional separation into 2 discrete types (conductive and/or sensorineural), defects in any of the anatomic parts comprising the ear translate into hearing loss.

In this review, we group relevant genodermatoses based on disorders of neural crest, metabolic, pigmentary, craniofacial and those lacking cutaneous findings. This division serves to guide the involved clinicians, be they dermatologists or ear, nose, and throat specialists, in appreciating clinical signs outside the scope of their expertise for proper diagnosis and subsequent management.

Figures were created using Microsoft visio.

#### Conflicts of interest

None disclosed.

#### REFERENCES

1. Shearer AE, Hildebrand MS, Smith RJH. Hereditary Hearing Loss and Deafness Overview. *GeneReviews*. Seattle, WA. University of Washington, Seattle. February 14, 1999. Updated July 27, 2017.
2. Caceres-Rios H, Tamayo-Sanchez L, Duran-Mckinster C, de la Luz Orozco M, Ruiz-Maldonado R. Keratitis, ichthyosis, and deafness (KID syndrome): review of the literature and proposal of a new terminology. *Pediatr Dermatol*. 1996;13(2):105-113.
3. Gironi LC, Colombo E, Brusco A, et al. Congenital sensorineural hearing loss and inborn pigmentary disorders: first report of multilocus syndrome in piebaldism. *Medicina (Kaunas)*. 2019; 55(7):345.
4. Keilmann A, Nakarat T, Bruce IA, Molter D, Malm G, Investigator HOS. Hearing loss in patients with mucopolysaccharidosis II: data from HOS—the Hunter Outcome Survey. *J Inherit Metab Dis*. 2012;35(2):343-353.
5. Wolf B, Spencer R, Gleason T. Hearing loss is a common feature of symptomatic children with profound biotinidase deficiency. *J Pediatr*. 2002;140(2):242-246.
6. Sunjtens E, Dreschler WA, Hess-Erga J, et al. Hearing loss in children with Fabry disease. *J Inherit Metab Dis*. 2017;40(5):725-731.
7. Lehalle D, Colombo R, O'Grady M, et al. Hearing impairment as an early sign of alpha-mannosidosis in children with a mild phenotype: report of seven new cases. *Am J Med Genet A*. 2019;179(9):1756-1763.
8. Cherian MP. Beta-mannosidase deficiency in two mentally retarded girls with intractable seizures. *Ann Saudi Med*. 2004; 24(5):393-395.
9. Corvino V, Apisa P, Malesci R, Laria C, Auletta G, Franzé A. X-linked sensorineural hearing loss: a literature review. *Curr Genomics*. 2018;19(5):327-338.

10. Jansen GA, Ofman R, Ferdinandusse S, et al. Refsum disease is caused by mutations in the phytanoyl-CoA hydroxylase gene. *Nat Genet.* 1997;17(2):190-193.
11. Kalyon S, Gökden Y, Demirel N, Erden B, Türkyılmaz A. Chanarin-Dorfman syndrome. *Turk J Gastroenterol.* 2019;30(1):105-108.
12. Pavani K, Reddy BSN, Singh BA. Rud's syndrome. *Indian Dermatol Online J.* 2014;5(2):173-175.
13. Bocangel MAP, Melo US, Alves LU, et al. Waardenburg syndrome: novel mutations in a large Brazilian sample. *Eur J Med Genet.* 2018;61(6):348-354.
14. Bassetto F, Tiengo C, Sferazza R, Belloni-Fortina A, Alaibac M. Vohwinkel syndrome: treatment of pseudo-ainhum. *Int J Dermatol.* 2010;49(1):79-82.
15. Abdollahi A, Hallaji Z, Esmaili N, et al. KID syndrome. *Dermatol Online J.* 2007;13:11.
16. Hegazi MA, Manou S, Sakr H, Camp GV. Unique autosomal recessive variant of palmoplantar keratoderma associated with hearing loss not caused by known mutations. *An Bras Dermatol.* 2017;92(5 suppl 1):154-158.
17. Richard G, Brown N, Ishida-Yamamoto A, Krol A. Expanding the phenotypic spectrum of Cx26 disorders: Bart-Pumphrey syndrome is caused by a novel missense mutation in GJB2. *J Invest Dermatol.* 2004;123(5):856-863.
18. Pierides AM, Athanasiou Y, Demetriou K, Koptides M, Deltas CC. A family with the branchio-oto-renal syndrome: clinical and genetic correlations. *Nephrol Dial Transplant.* 2002;17(6):1014-1018.
19. Chang CC, Steinbacher DM. Treacher Collins syndrome. *Sem Plast Surg.* 2012;26(2):83-90.
20. Koca TT. Apert syndrome: a case report and review of the literature. *North Clin Istanbul.* 2016;3(2):135-139.
21. Christiansen AG, Koppelhus U, Sommerlund M. Skin abnormalities in CHILD syndrome successfully treated with pathogenesis-based therapy. *Acta Derm Venereol.* 2015;95(6):752-753.
22. Posey JE, Burrage LC, Campeau PM, et al. Adult presentation of X-linked Conradi-Hünermann-Happle syndrome. *Am J Med Genet A.* 2015;167(6):1309-1314.
23. Sasaki H, Yanagi K, Ugi S, et al. Definitive diagnosis of mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome caused by a recurrent de novo mutation in the POLD1 gene. *Endocrine J.* 2018;65(2):227-238.
24. Avila M, Dymont DA, Sagen JV, et al. Clinical reappraisal of SHORT syndrome with PIK3R1 mutations: toward recommendation for molecular testing and management. *Clin Genet.* 2016;89(4):501-506.
25. Shiloh Y, Litvak G, Ziv Y, et al. Genetic mapping of X-linked albinism-deafness syndrome (ADFN) to Xq26.3-q27.1. *Am J Hum Genet.* 1990;47(1):20-27.
26. Gupta M. Dyschromatosis universalis hereditaria with sensorineural hearing loss. *Egypt J Dermatol Venerol.* 2016;36:26-27.
27. Farooq M, Moustafa RM, Fujimoto A, et al. Identification of two novel mutations in SLC29A3 encoding an equilibrative nucleoside transporter (hENT3) in two distinct Syrian families with H syndrome: expression studies of SLC29A3 (hENT3) in human skin. *Dermatology.* 2012;224(3):277-284.
28. Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet.* 2009;373(9879):1974-1986.
29. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA. Cockayne syndrome: clinical features, model systems and pathways. *Ageing Res Rev.* 2017;33:3-17.
30. Viana LM, Seyyedi M, Brewer CC, et al. Histopathology of the inner ear in patients with xeroderma pigmentosum and neurologic degeneration. *Otol Neurotol.* 2013;34(7):1230-1236.
31. Zhu H, Shang D, Sun M, et al. X-linked congenital hypertrichosis syndrome is associated with interchromosomal insertions mediated by a human-specific palindrome near SOX3. *Am J Hum Genet.* 2011;88(6):819-826.
32. Mamlouk MD, Zimmerman B, Mathes EF, Rosbe KW. Hearing loss in PHACE syndrome: clinical and radiologic findings. *Childs Nerv Syst.* 2018;34(9):1717-1724.
33. Roth DA, Hildesheimer M, Bardenstein S, et al. Preauricular skin tags and ear pits are associated with permanent hearing impairment in newborns. *Pediatrics.* 2008;122(4):e884-e890.
34. Kreicher KL, Weir FW, Nguyen SA, Meyer TA. Characteristics and progression of hearing loss in children with Down syndrome. *J Pediatr.* 2018;193:27-33.e2.
35. Alves C, Oliveira CS. Hearing loss among patients with Turner's syndrome: literature review. *Braz J Otorhinolaryngol.* 2014;80(3):257-263.
36. Siddiqi S, Siddiqi S, Mansoor A, et al. Novel mutation in AAA domain of BCS1L causing Bjornstad syndrome. *J Hum Genet.* 2013;58(12):819-821.
37. Sarkozy A, Conti E, Digilio MC, et al. Clinical and molecular analysis of 30 patients with multiple lentigines Leopard syndrome. *J Med Genet.* 2004;41(5):e68.
38. Kuemmerle-Deschner JB, Koitschev A, Tyrrell PN, et al. Early detection of sensorineural hearing loss in Muckle-Wells syndrome. *Pediatr Rheumatol Online J.* 2015;13(1):43.
39. Hopsu E, Aarnisalo A, Pitkaranta A. Progressive stapedial fixation in Beckwith-Wiedemann syndrome. *Arch Otolaryngol Head Neck Surg.* 2003;129(10):1131-1134.
40. Kantaputra PN, Sittiwangkul R, Sonsuwan N, Romanelli V, Tenorio J, Lapunzina P. A novel mutation in CDKN1C in sibs with Beckwith-Wiedemann syndrome and cleft palate, sensorineural hearing loss, and supernumerary flexion creases. *Am J Med Genet A.* 2013;161A(1):192-197.
41. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. *Eur J Hum Genet.* 2010;18(1):8-14.
42. Álvarez-Satta M, Castro-Sánchez S, Valverde D. Alström syndrome: current perspectives. *Appl Clin Genet.* 2015;8:171-179.
43. Weir FW, Hatch JL, Muus JS, Wallace SA, Meyer TA. Audiologic outcomes in Ehlers-Danlos syndrome. *Otol Neurotol.* 2016;37(6):748-752.
44. van Dijk FS, Cobben JM, Kariminejad A, et al. osteogenesis imperfecta: a review with clinical examples. *Mol Syndromol.* 2011;2(1):1-20.
45. Shin JJ, Hartnick CJ. Otologic manifestations of ectodermal dysplasia. *Arch Otolaryngol Head Neck Surg.* 2004;130(9):1104-1107.
46. Kumar P, Sharma PK, Kar HK. Olmsted syndrome. *Indian J Dermatol.* 2008;53(2):93-95.
47. Schweitzer DN, Yano S, Earl DL, Graham JM Jr. Johnson-McMillin syndrome, a neuroectodermal syndrome with conductive hearing loss and microtia: report of a new case. *Am J Med Genet A.* 2003;120A(3):400-405.
48. Martinelli D, Travaglini L, Drouin CA, et al. MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy. *Brain.* 2013;136(3):872-881.
49. Campeau PM, Kasperaviciute D, Lu JT, et al. The genetic basis of DOORs syndrome: an exome-sequencing study. *Lancet Neurol.* 2014;13(1):44-58.
50. Rigueur D, Roberts RR, Bobzin L, Merrill AE. A requirement for FGFR2 in middle ear development. *Genesis.* 2019;57(1):e23252.
51. Isaacson B. Anatomy and surgical approach of the ear and temporal bone. *Head Neck Pathol.* 2018;12(3):321-327.
52. Minoux M, Kratochwil CF, Ducret S, et al. Mouse Hoxa2 mutations provide a model for microtia and auricle duplication. *Development.* 2013;140(21):4386-4397.

53. Nishimura Y, Kumoi T. The embryologic development of the human external auditory meatus. *Acta Otolaryngol.* 1992; 112(3):496-503.
54. Lalani SR, Hefner MA, Belmont JW, Davenport SLH. CHARGE syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews.* 2006 Oct 2. Updated February 2, 2012.
55. Blake KD, Davenport SL, Hall BD, et al. CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila).* 1998;37(3):159-173.
56. Amin N, Sethukumar P, Pai I, Rajput K, Nash R. Systematic review of cochlear implantation in CHARGE syndrome. *Cochlear Implants Int.* 2019;20(5):266-280.
57. Chetty M, Roberts TS, Elmubarak M, Bezuidenhout H, Smit L, Urban M. CHARGE syndrome: genetic aspects and dental challenges, a review and case presentation. *Head Face Med.* 2020;16(1):10.
58. Richter CA, Amin S, Linden J, Dixon J, Dixon MJ, Tucker AS. Defects in middle ear cavitation cause conductive hearing loss in the Tcof1 mutant mouse. *Hum Mol Genet.* 2010;19(8):1551-1560.
59. Finch PW, Rubin JS, Miki T, Ron D, Aaronson SA. Human KGF is FGF-related with properties of a paracrine effector of epithelial cell growth. *Science.* 1989;245(4919):752-755.
60. Goh LC, Azman A, Siti HBK, et al. An audiological evaluation of syndromic and non-syndromic craniosynostosis in pre-school going children. *Int J Pediatr Otorhinolaryngol.* 2018;109:50-53.
61. Rajenderkumar D, Bamiou D, Sirimanna T. Management of hearing loss in Apert syndrome. *J Laryngol Otol.* 2005;119(5): 385-390.
62. Benjamin LT, Trowers AB, Schachner LA. Successful acne management in Apert syndrome twins. *Pediatr Dermatol.* 2005;22(6):561-565.
63. Murisier F, Guichard S, Beermann F. The tyrosinase enhancer is activated by Sox10 and Mitf in mouse melanocytes. *Pigment Cell Res.* 2007;20(3):173-184.
64. Ritter KE, Martin DM. Neural crest contributions to the ear: implications for congenital hearing disorders. *Hear Res.* 2019; 376:22-32.
65. Mammano F. Inner ear connexin channels: roles in development and maintenance of cochlear function. *Cold Spring Harb Perspect Med.* 2019;9(7):a033233.
66. Kam E, Melville L, Pitts JD. Patterns of junctional communication in skin. *J Invest Dermatol.* 1986;87(6):748-753.
67. Sharda S, Paliwal V, Chaturvedi P, Kuldeep C. Vohwinkel's syndrome in three siblings—a case report. *Indian J Paediatr Dermatol.* 2019;20:285.