DOI: 10.1111/pde.13713

WILEY Pediatric Dermatology

Biology of human melanocyte development, Piebaldism, and Waardenburg syndrome

Mohammed D. Saleem MD, MPH

University of Florida College of Medicine, Gainesville, Florida

Correspondence
Mohammed D. Saleem, MD, MPH,
University of Florida College of Medicine, Gainesville, FL.
Email: msaleem@g.clemson.edu

Abstract

Melanocyte development is orchestrated by a complex interconnecting regulatory network of genes and synergistic interactions. Piebaldism and Waardenburg syndrome are neurocristopathies that arise from mutations in genes involved in this complex network. Our understanding of melanocyte development, Piebaldism, and Waardenburg syndrome has improved dramatically over the past decade. The diagnosis and classification of Waardenburg syndrome, first proposed in 1992 and based on phenotype, have expanded over the past three decades to include genotype. This review focuses on the current understanding of human melanocyte development and the evaluation and management of Piebaldism and Waardenburg syndrome. Management is often challenging and requires a multidisciplinary approach.

KEYWORDS
depigmentation, hypomelanosis, leukoderma, melanocyte development, piebald trait, piebaldism, Waardenburg syndrome

1 | INTRODUCTION

Melanocyte development is coordinated by a network of genes that function in a temporal, spatial, and dose-dependent manner. Germline mutations in genes that regulate melanocyte development occur in patients with Piebaldism and Waardenburg syndrome (WS). Over the last three decades, our understanding of Piebaldism and WS has improved and continues to evolve with advancing molecular techniques. The identification of multiple novel genes has enhanced our ability to detect these disorders and prevent associated complications. The purpose of this article was to provide a comprehensive review of our current understanding of melanocyte development in humans and their related genodermatoses. We begin with a review of melanocyte development and subsequently describe a clinical approach to evaluating and managing patients with Piebaldism or Waardenburg syndrome.

2 | SEARCH STRATEGY AND SELECTION CRITERIA

Articles referenced in this manuscript were identified by MEDLINE using the Medical Subject Headings search tool for Piebaldism and Waardenburg syndrome. Additional search queries were performed and included the following key words: "piebald," "white forelock," "KIT," "c-KIT," "CD117," "PAX3," "SNAI2," "SLUG," "MITF," "SOX10," "EDNRB," "KITLG," "EDNRB," "EDN3," "Endothelin," "Kallmann syndrome," "PCWH," "Peripheral demyelinating neuropathy, central demyelination, Waardenburg syndrome and Hirschsprung disease," and "cochlear development." The search was limited to English articles indexed between May 1, 1995, and May 1, 2017. The bibliography of high-impact articles was reviewed to identify additional relevant studies and was included in our references when appropriate.

3 | MELANOCYTE DEVELOPMENT

The melanocyte is derived from the neural crest, a transient layer of multipotent embryonic cell population that gives rise to an array of cells and structures, including melanocytes, neurons, glial cells, and the enteric nervous system and facial skeleton.[1] Initially, melanocyte-derived neural crest cells were shown to migrate along a dorso-lateral pathway, between the dermamyotome and ectoderm, before diving ventrally (through the dermis) to populate the basal layer of the epidermis and hair follicles.[2] In 2009, Adameyko et al,[3] provided

evidence to show a substantial number of cutaneous melanocytes are derived from the Schwann cell precursors of nerves that innervate the skin. Phenotypic analysis of congenital birthmarks has now led to a new theory that proposes the existence of a novel population of melanocyte-derived precursor cells arising within the mesoderm that follow a centrifugal migration pattern.[3] The origin of melanocytes is complex and the differences in origin may about for the variable phenotype exhibited by various disease processes.[4]

In humans, melanocytes can be found in the skin, eyes, and cochlea. In the epidermis and iris, melanocytes are responsible for the variation in skin and eye color, respectively.[2,5,6] In the stria vascularis of the inner ear, they exist as intermediate cells that help maintain an electrochemical potential necessary for normal hearing.[7-9] The development, survival, and migration of melanocyte precursors during embryogenesis are orchestrated by a complex regulatory network of genes that include *MITF*, *PAX3*, *SOX10*, *EDNRB*, *EDN*, *KIT*, and *SNAI2* (Figure 1).

Microphthalmia transcription factor (MITF) protein is termed the "master transcription regulator" because it is essential for melanocyte survival, migration, proliferation, and differentiation.[10,11] In the melanocyte lineage, various transcription factors (eg, PAX3, SOX10) and

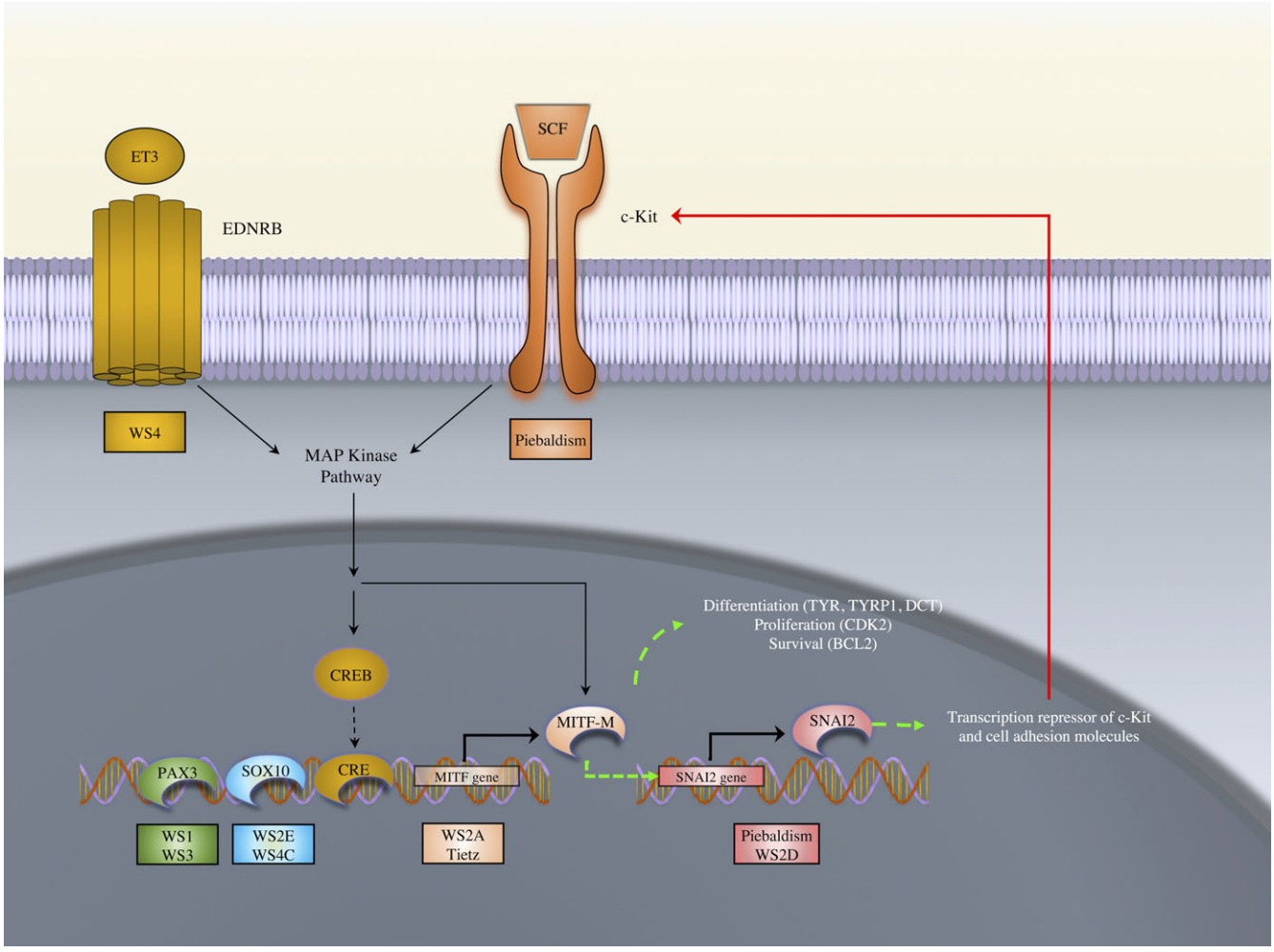


FIGURE 1 Melanocyte development. The *MITF* gene encodes a basic helix-loop-helix leucine zipper (b-HLH-Zip) dimeric nuclear transcription factor essential for the survival, migration, proliferation, and differentiation of multiple cell lines.[100,101] Nine unique promotor-exon units have been identified and are important in synthesizing several isoforms with distinct 5′ exons. The M-isoform is expressed exclusively in the melanocytes lineage. *MITF-M* transcription is regulated by multiple transcription factors including, PAX3, SOX10, LEF, CREB, and MITF. Wnt signaling (not show) is critical for melanocyte development by promoting the interaction between ß-catenin with LEF1/TCF, which induces the MITF-M promotor.[10,101] Furthermore, the b-HLH-Zip domain of MITF interacts with LEF-1, functioning as a nuclear mediator to attenuate MITF expression and regulating gene dosage (not shown).[103] PAX3 and SOX10 trans-activate the MITF promoter, synergistically upregulating expression.[2,113] MITF effector genes, including SNAI2, Bcl2, p16, and proteins of melanogenesis.[100,114] SNAI2 is a transcription regressor of c-Kit and E-cadherin gene, which are important for normal migration of melanoblasts and maintaining hemostasis.[115-123] The negative feedback loop between c-Kit and SNAI2 is essential for maintaining homeostasis; overexpression of either impairs self-renewal ability of these cells.[120,121] The loss or reduction in the expression of Bcl2 and p16 tumor suppressor genes would explain the rapid depletion of melanocyte stem cells in the follicles and subsequent hair graying.[124-127] SOX10, EDN3, and EDNRB, in addition to the melanocyte neural crest-derived cells, are critical genes for enteric neural crest-derived cell proliferation, migration, and survival. Mutations in any of these three genes can result in the absence of melanocytes and neurons in the skin and gut, respectively[128-130]

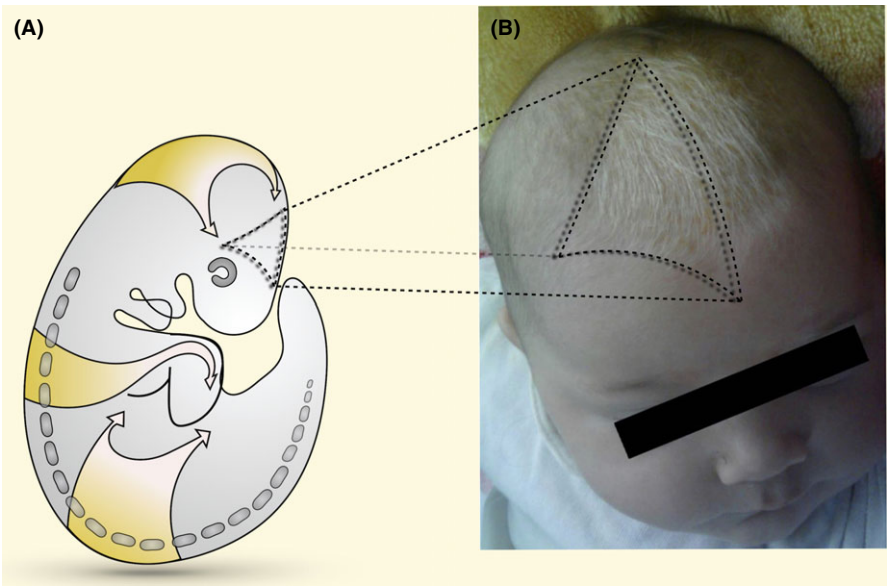


FIGURE 2 White forelock. Melanocytes arise from neural crest cells that reside at the top or "crest" of the neural tube. From this point, the melanocyte-derived neural crest cells migrate, proliferate, and differentiate along a dorso-lateral pathway, before diving ventrally to reach its most distant site.[2] As a result, gene defects in melanocyte development result in abnormal pigment patterns that are prominent at midline, the point farthest from the site of embryologic origin. The clinical photo of the child with the white forelock (Figure 2B) was adapted from Kerkeni et al[131].

extracellular signaling pathways (eg, KIT, EDNRB-EDN) regulate the expression of *MITF*.[10] In addition to melanocyte precursors, PAX3, SOX10, EDNRB, and EDN are broadly expressed in several other lineages of neural crest cells. Early expression of PAX3 is critical for the development of melanocytes, craniofacial tissue, and formation of the upper limbs.[12,13] SOX10, EDNRB, and EDN are necessary for the normal migration of melanocyte-derived and enteric-derived neural crest cells to the skin and gut, respectively.[14] Loss-of-function mutations in *MITF* or its regulatory genes can cause a striking pattern of depigmentation characteristic of Piebaldism and Waardenburg syndrome.

4 | PIEBALDISM AND WAARDENBURG SYNDROME

Piebaldism and Waardenburg syndrome (WS) are neurocristopathies characterized by incomplete penetrance and high levels of variable expressivity.[15-18] A white forelock is the most common cutaneous manifestation of both conditions and can be the sole integumentary finding.[17,19] Depigmented patches, when present, are frequently apparent at birth, lack convex borders, and classically involve the forehead, ventral trunk, and midextremities (Figure 2). Hyperpigmented macules adjacent to and/or within depigmented patches are a classic characteristic finding that can aid in the diagnosis of Piebaldism.[19-22] Axillary freckling and café-au-lait spots are occasional features of Piebaldism and should not be confused with neurofibromatosis-1.[23-27] Piebaldism is best viewed as a variant of Waardenburg syndrome without the extra-cutaneous manifestations.

Waardenburg syndrome (WS) is an auditory-pigmentary disorder that accounts for 2%-3% of congenital deafness. The estimated worldwide incidence is 2 to 3 cases per 100 000 population and equally affecting both genders and all races.[28,29] There are four subtypes of WS that are defined phenotypically. The diagnosis of WS1 can be established clinically using the Waardenburg Consortium criteria (Table 1).[30] WS2, WS3, and WS4 are defined by the absence of dystopia canthorum (ie, lateral displacement of the inner canthi), presence of musculoskeletal abnormalities, and aganglionic megacolon, respectively.[31] The advancements in molecular techniques and the identification of multiple pathogenic genes have allowed the traditional classification to be further subdivided by genotype (Table 2).

TABLE 1 Waardenburg syndrome type I diagnostic criteria proposed by Waardenburg consortium[30]

Waardenburg syndrome type I diagnostic criteria[a]	
Major criteria	**Minor criteria**
Congenital sensorineural hearing loss	Cutaneous hypopigmentation
White forelock	Synophrys or medial eyebrow flare
Abnormal iris pigment[b]	Broad/high nasal root or low columella
Dystopia canthorum (W index > 1.95)[c]	Hypoplastic nasal alae
Affected first-degree relative	Premature gray hair (< 30 y of age)[d]

[a]Requires 2 major criteria or 1 major plus 2 minor criteria.
[b]Complete heterochromia iridum, partial heterochromia, or hypoplastic blue irides (brilliant blue irides).
[c]W index = X + Y + (a ÷ b); where X = (2a − 0.2119c + 3.909) ÷ c and Y = (2a − 0.2479b + 3.909) ÷ b. a, b, and c are the dimensions, measured in millimeters, of the inner canthal, interpupillary, and outer canthal.
[d]Defined by graying before 30 years of age.

5 | EVALUATION

Piebaldism and WS should be considered in infants or young children with stable, midline, depigmented patches (Figure 2). Phenotypic severity ranges from a few depigmented strands of hair to diffuse depigmentation.[15,32-34] The use of hair dye should be specifically inquired about, otherwise the leukotrichia can go unrecognized.

TABLE 2 Genodermatoses associated with defects in melanocyte development

Type	Gene	Location	MIM	Inheritance	Comment[a]
Piebaldism	*KIT* *SNAI2*	4q12 8q11.21	172 800	AD	Café-au-lait spots and axillary freckling may be present. Mild cases are associated with haploinsufficiency; in contrast, a dominant-negative mutation of the tyrosine kinase domain, manifests with a severe phenotype Homozygous mutations in Kit or SNAI can result in WS2.
WS1	*PAX3*	2q36.1	193 500	AD	52% hearing loss Vestibular dysfunction (> 50%); even when hearing is normal[132] Craniofacial abnormalities and other[b] neural crest-related defects are rare.
WS3[c]	*PAX3*	2q36.1	148 820	AD, AR	57% hearing loss WS1[d] plus musculoskeletal abnormalities of the upper limbs (Flexion contractures, musculoskeletal hypoplasia, and/or syndactyly)[133,134]
WS2	*MITF*	3p13	193 510	AD	90% hearing loss High frequency of early hair graying and excessive freckling[135,136]
	SNAI2	8q11.21	608 890	AR	Only 2 cases reported that resulted from homozygous SNAI2 deletions. Both had sensorineural hearing loss and heterochromia, without any cutaneous or dysmorphic manifestations.[115] Since the initial publication in 2002, no additional confirmatory cases have been reported.
	SOX10	22q13.1	611 584	AD	100% hearing loss Often arise de-novo[60,110,135,137] Chronic constipation[49,66,96] Hyponosmia/Anosmia[56,66] Inner[f] ear malformations and temporal bone abnormalities[56,65,138,139]
	EDNRB	13q22.3	Ref. 140 (Issa 2017)	AD	70% hearing loss[140] Predicted to account for 5%-6% of WS2 cases Reported from 6 families in France. None had cutaneous depigmentation; but a white lock and early graying were present in 1/11 and 2/11 cases, respectively. Segmental heterochromia was found at a high proportion.
	KIT	4q12	Ref. 141	AR	Complete depigmentation of the skin and hair. Hearing loss, brilliant blue irides, hypotonia, and motor and language delay. The proband parents both had classical features of piebaldism.
	KITLG[e]	12q21.32	Ref. 142,143	Unknown	Only two publications identified with potential confounders. They presented similar to other subjects with WS2; however, café-au-lait spots were also present.

(Continues)

The pattern of depigmentation and/or presence of a white forelock helps to differentiate them from vitiligo and other hypopigmented conditions of the newborn (Table 3). Chromosome 4q12q21 deletions can be mistaken for Waardenburg syndrome because of the identical pattern of skin depigmentation, a white forelock, and craniofacial abnormalities (A functional loss in the *KIT* gene, which lies within this chromosomal region, explains the phenotypic resemblance.)[39-42] However, hypotonia, intellectual disability, and growth abnormalities are evident in nearly all patients, but are rarely features of WS.[43,44] A skin biopsy is not necessary or adequate in confirming the diagnosis of WS.[45,46]

5.1 | Assessment

A suspected diagnosis of Piebaldism or WS should be accompanied by a thorough history and physical examination (Figure 3). A family history is important in identifying familial cases and should focus on pigment abnormalities, premature graying of the hair, hearing loss, and gastrointestinal complications. A proband with WS4 may have a sibling with chronic constipation, recurrent enterocolitis, or early death from intestinal complications.[47,48] Newborns suspected of having WS should not be released from the hospital until they have passed stool. During the neonatal period, the presence of abdominal distension, bilious emesis, and poor feeding are red flags suggestive of Hirschsprung disease (HD). Mild cases of HD typically manifest in older children with severe chronic constipation.[48,49] As such, a low threshold for referral for a rectal suction biopsy is warranted.[50]

A detailed physical examination should be performed with particular attention to the craniofacial structures, genitalia, and potential neurological symptoms, including any delay in the developmental milestones. Anosmia, eunuchoidal proportions, cryptorchidism, or a micropenis should prompt a formal evaluation for Kallmann's syndrome, a form of congenital hypogonadotropic hypogonadism (CHH) that can result from *SOX10* mutations (Table 4).[51,52] In an infant male with a micropenis or

TABLE 2 (Continued)

Type	Gene	Location	MIM	Inheritance	Comment[a]
WS4	*EDNRB*	13q22.3	277 580	AD, AR	54% hearing loss Severe[g] variant (ABCD syndrome) with black forelock
	EDN3	20q13.32	613 265	AR	AD mutations result in HSCR only 75% hearing loss
	SOX10	22q13.1	600 423	AD	93% hearing loss Skin depigmentation might be most frequent and severe with WS4.[45,144-146]
PCWH[h]	*SOX10*	22q13.1	609 136	AD	WS2 or WS4 plus leukodystrophy and/or peripheral neuropathy[147,148]
Tietz[i] *syndrome*	*MITF*	3p13	103 500	AD	Congenital sensorineural hearing loss and global[f] hypopigmentation Premature graying of the hair and diffuse freckling in sun-exposed regions occur in a majority of cases.

The traditional classification of Waardenburg syndrome is based on phenotype. WS1 and WS3 are caused by pathogenic variants in the *PAX3* gene. WS2 and WS4 can be further subdivided by genotype. The majority of WS2 cases do not have an identifiable pathogenic genel.[97] While *MITF* and *SOX10* mutations account for approximately 30% of cases, SNAI2, EDNRB, and KITLG are rare and account for less than 5% of cases.[98,99] Pathogenic variants of SOX10 and EDNRB-EDN3 account for approximately 50% and 30% of WS4 cases, respectively.

EDN, Endothelin; EDNRB, Endothelin-B Receptor; HSCR, Hirschsprung disease; PCWH syndrome, Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease; WS, Waardenburg syndrome.

[a]Hearing loss percentages based on a systematic review Song 2016.[149]

[b]Few human reports of Spina bifida[150,151]; Synophrys, cleft lip and cryptochidism[152]; Anal Atresia[153]; Choroidal Melanoma[154]; Unilateral renal agenesis[155]; congenital cataracts[156]. In mice, PAX3 mutations induce pigment defects, spina bifida, and heart defects (Truncus arteriosus).[157,158]

[c]Multiple reports demonstrate WS3 phenotype resulting from parents with heterozygous mutations in PAX3 (with WS1) producing a proposita that is homozygous with WS3 phenotype. The phenotype in the AR cases was extremely severe, with nearly complete depigmentation (with only small areas of normal skin) and severe contractures of the upper limbs with muscle atrophy.[134,159]

[d]Recently, IHH and EPHA4 haploinsufficiency have been suggested as the genes responsible for syndactyly and short stature associated with WS3, both lie in close proximity to PAX3 gene.[160,161]

[e]Report was from a single family. KITLG encodes a soluble and transmembrane isoform. The mutation was in exon 4, a section of the gene sequence shared by both soluble and transmembrane KITL after alternative splicing. It is plausible that we have never seen it as a cause before because of the rare nature of affecting both isofroms.[142] Interestingly, familial progressive hyper- and hypopigmentation (FPHH) is another genetic pigmentary disease associated with KITLG mutations (OMIM 145 260).

[f]Radiologically, enlarged vestibule and cochlear deformity associated with bilateral agenesis or hypoplasia of semicircular canals is highly suggestive of WS with SOX10 mutations.[65]

[g]Albinism, Black Lock, Cell Migration Disorder (ABCD) syndrome, described in a Turkish family, see Ref. 162,163.

[h]PCWH, WS4, and WS2 resulting from SOX10 mutation might best be viewed as a spectrum. Many subjects classified as WS2 with SOX10 mutations have severe constipation or neurological symptoms.[49,164,165] Hypopigmented macules might be a feature suggestive of WS associated with SOX10 mutations, rather than the classical midline depigmentation; however, a white forelock is still often reported.[166]

[i]Tietz syndrome is caused by a heterozygous mutation in exon 7 of MITF. Unlike Waardenburg syndrome, skin melanocyte density is normal (suggesting that the migration of melanocyte precursors during embryogenesis is normal). In contrast to albinism, visual acuity is normal in all the reported cases. Premature graying and development of freckles on sun-exposed skin appear to be characteristic features.[104,105,167,168]

undescended testes, a magnetic resonance image (MRI) can be used as a primary diagnostic method.[53,54] MRI in subjects with WS and *SOX10* pathogenic variants frequently reveals hypoplasia or aplasia of the olfactory bulbs; in addition, inner ear or temporal bone abnormalities are often present.[55-67] In older children, an MRI is often unnecessary and formal testing for anosmia or hyposomia can establish the diagnosis of Kallmann's syndrome.[68] Unfortunately, CHH is a challenging diagnosis that is often made late in adolescence or adulthood. A careful evaluation, early diagnosis, and prompt referral can reduce numerous complications that occur later in life.[51]

6 | MANAGEMENT

6.1 | General

The management of Piebaldism and Waardenburg syndrome involves a multidisciplinary team approach, patient education, and early intervention in selected patients. All patients with WS, and their families, should be offered genetic counseling and testing. The pathogenic PAX3 alleles may increase the risk of severe neural tube defects in the probands offspring; whether this risk is folate-response is unknown.[69] Regardless, daily folic acid supplementation (0.4-0.8 mg) is recommended to all women of childbearing age.[70]

6.2 | Integumentary system

Skin depigmentation associated with Piebaldism and WS is stable, but lacks melanocytes and inflammation; as a result, light therapy and corticosteroids have no role in therapy. Optimal skin photo-protection should be recommended. Management with cosmetic camouflage and hair dye can improve quality of life and provide significant emotional benefit.[71-73] Tissue grafting and cell transplantation have high success rates for the depigmented patches of Piebaldism.[74-84] The literature for depigmented patches associated with WS is

TABLE 3 Major differential diagnoses for Piebaldism and Waardenburg syndrome

Condition	Features
Vitiligo[169,170]	Segmental: Rapid onset then stabilizes; asymmetrical, trigeminal, and thoracic are frequent sites; involved segments do not cross midline Nonsegmental: Progressive with flares; symmetrical
Nevus anemicus	Irregular borders, interspersed normal; pallor becomes less pronounced under Woods lamp;[171] diascopy[a] can be diagnostic
Nevus[b,c] depigmentosus	Isolated, multiple, or segmental,[172] most common differential encountered in vitiligo clinics,[173] poor response to surgical grafts[174-176] Woods light demonstrates off-white accentuation; in contrast to chalk white seen with depigmentation conditions (eg, Piebaldism)
Tuberous[d] sclerosis complex (TSC)[177]	Hypopigmented macules of tuberous sclerosis can be round, oval, segmental, or ash-leaf shaped; additional cutaneous (eg, shagreen patches, angiofibromas) or neurological (eg, seizures) features are often present
Hypomelanosis of Ito (Pigmentary Mosaicism)[178]	Linear distribution, streaks, or whorls; majority of cases occur sporadically Biopsy typically reveals a normal number of melanocytes Approximately 73% have extra-cutaneous manifestations (eg, developmental delay, skeletal deformities, epilepsy, intellectual disability)
Chr 4q12q21 deletions	Midline depigmentation, intellectual disability, hypotonia, and/or growth abnormalities

[a]Diascopy can be performed by applying pressure to the patch and surrounding skin with a glass slide. It differentiates vascular abnormalities from other conditions. Visualizing an erythematous change in only normal skin when pressure is applied to the patch is characteristic of nevus anemicus.[179,180]
[b]Nevus depigmentosus might be considered a mild state of mosaicism, and it can be difficult to differentiate from hypopigmented macules associated with TSC.[181,182]
[c]The diagnosis of indeterminate or borderline leprosy should be considered in the differential of nevus depigmentosus in high-risk children; its prevalence is similar to that of ND in some areas and can present with similar findings.[183]
[d]The prevalence of hypopigmented macules in the healthy population is approximately 5%; however, they can also be the initial manifestation of TSC. In the absence of a positive family history for TSC or additional symptoms, further workup is unnecessary.[184]

anecdotal, but theoretically should be similar to Piebaldism. Of note, the dermatologist should be aware that monopolar diathermy should not be used in the head and neck region of patients with cochlear implants (which these patients often have). Bipolar diathermy can be used at distances greater than 2 cm away from the implant.[85] Electrical current can result in damage to the implant, further surgery, additional expenses, and possible complications.

6.3 | Auditory system

Waardenburg syndrome is a high-risk indicator for hearing loss; as such, even if the newborn screening is passed, the American Academy of Pediatrics recommends a referral for at least one diagnostic auditory assessment.[86] The comprehensive audiological evaluation should be performed no later than 3 months of age. Confirmed hearing loss requires appropriate referral (otolaryngology, speech-language pathology, audiology, genetics) and intervention by no later than 6 months of age.[87] Congenital sensorineural hearing loss treated with cochlear implants improves language, communication, and cognitive skills.[88-93] At least 2 weeks prior to cochlear implant placement, in addition to routine age-specific vaccinations, the child should receive pneumococcal vaccines (PCV13 and/or PPSV23) because of the heightened risk for bacterial meningitis.[94,95]

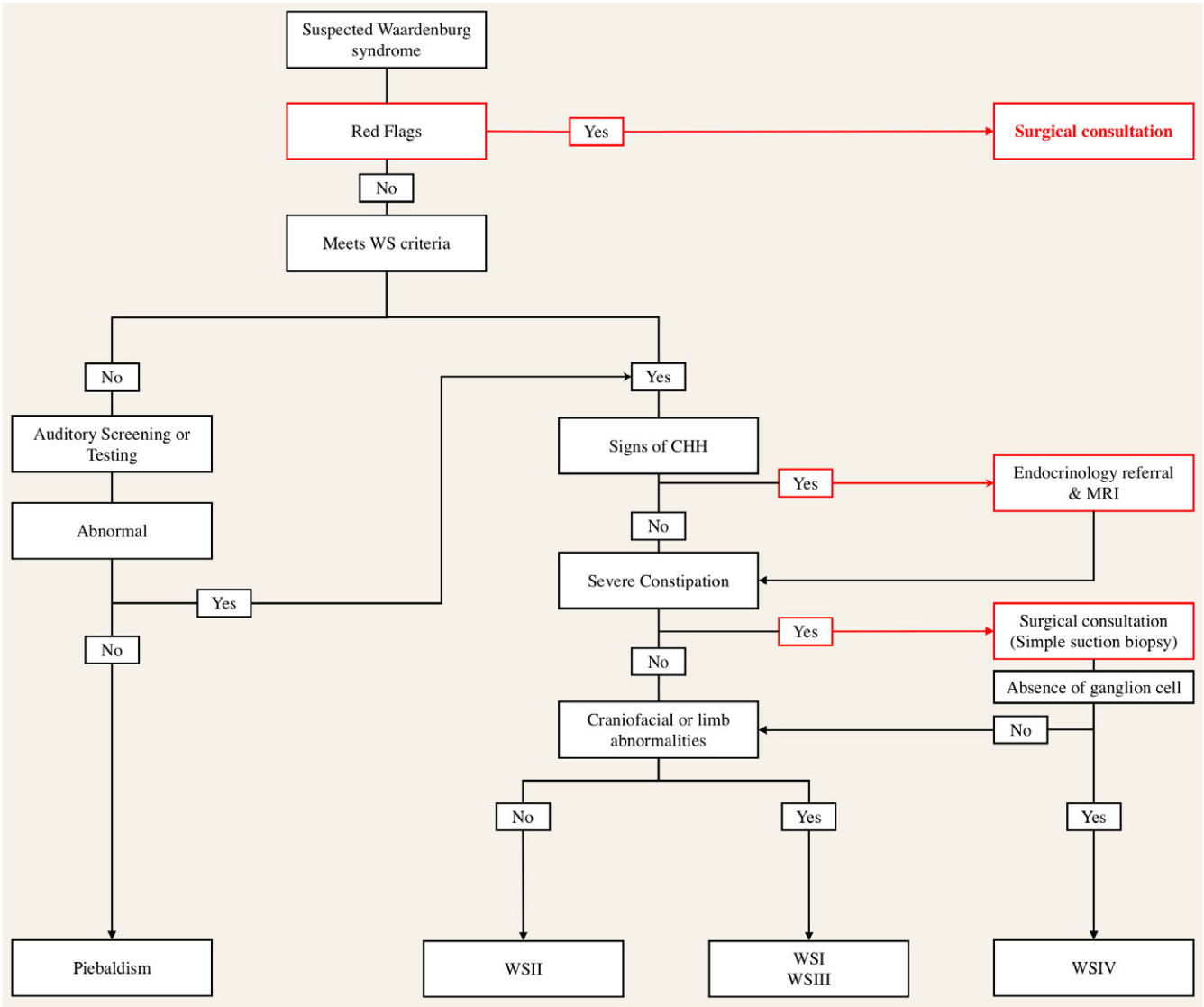
6.4 | Gastrointestinal system

During follow-up visits, the patient should be asked about constipation because HD may not be apparent early in life. Chronic constipation should prompt a referral for an evaluation of HD. A diagnostic biopsy suggestive of HD is treated with surgical anastomosis of functional gut.[14] Chronic constipation and negative diagnostic tests for HD have been described with SOX10 mutations.[49,96] Even within the same family, rectal biopsy can be positive in one offspring, but negative in another with chronic constipation and an identical SOX10 mutations.[66]

7 | PERSPECTIVES, AREAS OF UNCERTAINTY, AND CONCLUSIONS

Our understanding of the development of melanocytes in humans has drastically improved over the last three decades. Greater than 90% of WS1 cases can be identified by single-gene testing (*PAX3* sequence analysis). The heterogeneous variations in genotype and phenotype associated with WS1 can be explained by haploinsufficiency that results from a loss-of-function mutation in *PAX3*, a dose-sensitive gene. A dominant-negative *PAX3* pathogenic variant or homozygous loss-of-function mutations produce a severe phenotype characteristic of WS3.

The majority (> 60%) of WS2 cases are unexplained at the molecular level.[97] Heterozygous *MITF* and *SOX10* mutations each account for 15% of cases; *SNAI2*, *EDNRB*, and *KITLG* are rare and account for less than 5%.[98,99] Proteins that activate or repress the expression of MITF-M are potential gene candidates. For instance, FOXD3, POU3F2, ALX3, TNF-α, and TGF-ß can reduce MITF-M levels; in contrast, genes involved in cAMP-CREB, Wnt, or MAPK signaling pathways can increase MITF expression.[100] Furthermore, post-translational modifications (eg, ubiquitination, phosphorylation)



Red Flags	
Evaluation	Findings
History	Bilious emesis, poor feeding, failure to pass meconium within 48 hours or severe constipation since birth
Physical examination	Abdominal distension Absence of stool in the rectal vault
Plain Radiograph	Dilated bowels and absence of rectal air
Contrast enema	Transition zone between normal and pathologic bowel

FIGURE 3 Evaluation of Piebaldism and Waardenburg syndrome (WS)

and chromatin complexes that mediate epigenetic remodeling (eg, DNA methylation, histone modifications) contribute to MITF regulation.[101,102] The increasing use of whole-genome sequencing will hopefully identify novel genes that are responsible for the unexplained cases of WS.

The primary mechanism of WS2 associated with *MITF* and *SOX10* pathogenic variants appears to be related to haploinsufficiency, and the degree of phenotype severity may also be related to Wnt signaling. *MITF* pathogenic variants that do not effect LEF-1 mediated activation of the M-promotor appear to be associated with a mild phenotype.[103] The most severe auditory-pigmentary phenotype, represented by Tietz syndrome, are associated with dominant-negative mutations in *MITF* or pathogenic variants that prevent LEF-1 site activation (eg, *MITF* p.R217I).[103-105] Homozygous mutations in MITF also

result in a severe phenotype characterized by coloboma, osteopetrosis, microphthalmia, macrocephaly, global hypopigmentation, and deafness (COMMAD).[106] Similarly, the most severe phenotype associated with pathogenic variants of SOX10, characterized by the presence of neuropathy, result from truncated mutations neighboring or involving the last exon.[107] The mechanism is thought to be related to the escape from nonsense-mediated mRNA decay and the production of a mutant protein that competes and impairs the function of the wild-type SOX10 protein.[60,96,108,109]

Lastly, the relationship between genotype and phenotype in humans continues to be a large area of uncertainty and primarily anecdotal. Many of the findings, especially in relation to PAX3 and SOX10 pathogenic variants, can be logically extrapolated from understanding their function during embryogenesis (Table 5). For instance, anosmia, chronic constipation, and inner ear malformations are likely specific phenotypic markers of *SOX10* pathogenic variants. A common limitation in many studies involving patients with WS is the absence of long-term follow-up and lack of awareness. In one series, 15 subjects with WS and SOX10 mutations were studied retrospective in order to better define its relationship to "temporal bone abnormalities." Bilateral agenesis of the olfactory bulbs was "incidentally" found in 7 of 8 subjects with adequate MR imaging sequences.[65] However, the subjects were prepubertal and formal testing for anosmia was not reported. Interestingly, SOX10 mutations, unlike PAX3 mutations, most commonly arise de-novo, which may be related to infertility.[110-112] Future studies focusing on genotype should include a comprehensive phenotype profile and, if appropriate, long-term follow-up. Currently, no nationally recognized guidelines specific for Piebaldism or Waardenburg syndrome exist.

TABLE 4 Signs of congenital hypogonadotropic hypogonadism (CHH)

Period assessed	Signs of congenital hypogonadotropic hypogonadism[a,b]
Mini-puberty[c]	M: Cryptorchidism, micropenis F: No specific signs
Adolescent	M/F: Eunuchoidal proportions, low libido, sexual function is lacking, hypo- or anosomnia M: Prepubertal testes, undervirilization, absent growth spurt F: Absent breast development, primary amenorrhea
Adulthood	Infertility, osteoporotic fractures

CHH: Congenital hypogonadotropic hypogonadism; M: Male; F: Female.
[a]CHH is a challenging diagnosis that is very often diagnosed late in adolescence or adulthood. A careful evaluation by the dermatologist can be very rewarding. Timely diagnosis and treatment accompany a long list of benefits. See Ref. 51 for further recommendations on diagnosis and treatment.
[b]All neonates born to parents with CHH should be formally evaluated by an endocrinologist. Referral should not be delayed because the window for hormone profiling is narrow.
[c]Mini-puberty: A phenomenon that refers to the period the HPG axis is active in utero and for the short period after birth. During this short period, hormone profiling at 4-8 wks can establish the diagnosis. Afterward, the diagnosis can be very difficult to establish prior to adolescence.

8 | OTHER RESOURCES

U.S. National Library of Medicine: https://ghr.nlm.nih.gov/condition/waardenburg-syndrome#synonyms.

American Society for Deaf Children: http://deafchildren.org.

The Leiden Open Variation Database includes the mutations that characterize Waardenburg syndrome and clinical variants: http://grenada.lumc.nl/LOVD2/WS/home.php?action=switch_db).

TABLE 5 Selective role of PAX3[185] and SOX10[66,186-188] in extra-cutaneous tissues during embryogenesis

Type	Extra-cutaneous function during embryogenesis	Phenotype
PAX3	Expressed in neural crest cells that contribute to the craniofacial structures	Lateral displacement of the medial canthi Cleft palate
	Expressed in myogenic precursors and important in their migration and survival to the limbs	Hypoplasia of the limb musculature of the upper extremities due to premature apoptosis
	Expressed in dark cell precursors that migrate to the vestibule and function in fluid homeostasis[189]	Vestibular symptoms[132] (eg, vertigo)
SOX10	Expressed in glial-derived neural crest cells and important in their survival and differentiation	Neuropathy and leukodystrophy due to hypo- or demyelination
	Expressed in the enteric-derived neural crest cells and important in the development of the enteric ganglia	Enteric hypo- or aganglionosis Chronic constipation
	Expressed in neural crest cells that are important in the development of the inner ear and temporal bone	Bilateral hypo- or aplasia of the semicircular canals Temporal bone abnormalities
	Important in the differentiation of neural crest-derived olfactory ensheathing cells and migration of GnRH neurons to the forebrain[188,190]	Olfactory bulb hypoplasia or aplasia (ansomia) Congenital hypogonadotropic hypogonadism

The Human Gene Mutation Database can be used to identify gene lesions associated with inherited conditions in humans: http://www.hgmd.cf.ac.uk/ac/index.php.

An extensive list of melanogenic genes in mice can be found at http://www.espcr.org/micemut/.

ACKNOWLEDGMENT

Special thanks to following experts for their detailed review of the initial draft and providing valuable suggestions: James Stallworth, Masahiro Hayashi.

ORCID

Mohammed D. Saleem https://orcid.org/0000-0003-3666-0230

REFERENCES

1. Mica Y, Lee G, Chambers SM, et al. Modeling neural crest induction, melanocyte specification, and disease-related pigmentation defects in hESCs and patient-specific iPSCs. *Cell Rep*. 2013;3(4):1140-1152.
2. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. *Nature*. 2007;445(7130):843-850.
3. Adameyko I, Lallemend F, Aquino JB, et al. Schwann cell precursors from nerve innervation are a cellular origin of melanocytes in skin. *Cell*. 2009;139(2):366-379.
4. Kinsler VA, Larue L. The patterns of birthmarks suggest a novel population of melanocyte precursors arising around the time of gastrulation. *Pigment Cell Melanoma Res*. 2018;31(1):95-109.
5. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev*. 2004;84(4):1155-1228.
6. Shields CL, Nickerson SJ, Al-Dahmash S, Shields JA. Waardenburg syndrome: iris and choroidal hypopigmentation. *JAMA Ophthalmol*. 2013;131(9):1167.
7. Tachibana M. Cochlear melanocytes and MITF signaling. *J Investig Dermatol Symp Proc*. 2001;6(1):95-98.
8. Kral A, O'donoghue GM. Profound deafness in childhood. *N Engl J Med*. 2010;363:1438-1450.
9. Steel KP, Kros CJ. A genetic approach to understanding auditory function. *Nat Genet*. 2001;27(2):143-149.
10. Hou L, Pavan WJ. Transcriptional and signaling regulation in neural crest stem cell-derived melanocyte development: do all roads lead to Mitf? *Cell Res*. 2008;18(12):1163-1176.
11. Tachibana M, Takeda K, Nobukuni Y, et al. Ectopic expression of MITF, a gene for Waardenburg syndrome type 2, converts fibroblasts to cells with melanocyte characteristics. *Nat Genet*. 1996;14(1):50-54.
12. Wildhardt G, Zirn B, Graul-Neumann LM, et al. Spectrum of novel mutations found in Waardenburg syndrome types 1 and 2: implications for molecular genetic diagnostics. *BMJ Open*. 2013;3(3):e001917.
13. Sauka-Spengler T, Bronner-Fraser M. A gene regulatory network orchestrates neural crest formation. *Nat Rev Mol Cell Biol*. 2008;9(7):557-568.
14. Heanue TA, Pachnis V. Enteric nervous system development and Hirschsprung's disease: advances in genetic and stem cell studies. *Nat Rev Neurosci*. 2007;8(6):466-479.
15. Oiso N, Fukai K, Kawada A, Suzuki T. Piebaldism. *J Dermatol*. 2013;40(5):330-335.
16. Zlotogora J. Penetrance and expressivity in the molecular age. *Genet Med*. 2003;5(5):347-352.
17. Milunsky JM. Waardenburg Syndrome Type I. 1993; http://www.ncbi.nlm.nih.gov/pubmed/20301703. Accessed March 18, 2017.
18. Haj Kassem L, Ahmado MF, Sheikh Alganameh M. A rare case of seven siblings with Waardenburg syndrome: a case report. *J Med Case Rep*. 2018;12(1):192.
19. Bassi A, Berti S, Galeone M. Piebaldism. *QJM*. 2015;108(11):915.
20. Narita T, Oiso N, Fukai K, et al. Two children with a mild or moderate piebaldism phenotype and a father without leukoderma in a family with the same recurrent missense mutation in the kinase domain of KIT. *Eur J Dermatol*. 2011;21(3):446-447.
21. Huang A, Glick SA. Piebaldism in history—"The Zebra People." *JAMA Dermatol*. 2016;152(11):1261.
22. Grob A, Grekin S. Piebaldism in children. *Cutis*. 2016;97(2):90-92.
23. Duarte A, Mota A, Baudrier T, et al. Piebaldism and neurofibromatosis: state of knowledge. *Dermatol Online J*. 2013;19(1):17.
24. Jia W-X, Xiao X-M, Wu J-B, et al. A novel missense KIT mutation causing piebaldism in one Chinese family associated with café-au-lait macules and intertriginous freckling. *Ther Clin Risk Manag*. 2015;11(5):635-638.
25. Stevens CA, Chiang P-W, Messiaen LM. Café-au-lait macules and intertriginous freckling in piebaldism: clinical overlap with neurofibromatosis type 1 and Legius syndrome. *Am J Med Genet Part A*. 2012;158A(5):1195-1199.
26. Sarma N, Chakraborty S, Bhanja D, Bhattachraya S. Piebaldism with non-intertriginous freckles: what does it mean?. *Indian J Dermatol Venereol Leprol*. 2014;80(2):162.
27. Ma J, Zhang T-S, Lin K, et al. Waardenburg syndrome type II in a Chinese patient caused by a novel nonsense mutation in the SOX10 gene. *Int J Pediatr Otorhinolaryngol*. 2016;85:56-61.
28. Orphanet: Waardenburg syndrome. https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=663&Disease_Disease_Search_diseaseGroup=waardenburg&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group of diseases=Waardenburg-syndrome&title=Waardenburg-syndrome&search=Disea. Accessed August 23, 2018.
29. Nayak CS, Isaacson G. Worldwide distribution of Waardenburg syndrome. *Ann Otol Rhinol Laryngol*. 2003;112(9 Pt 1):817-820.
30. Farrer LA, Grundfast KM, Amos J, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: first report of the WS consortium. *Am J Hum Genet*. 1992;50(5):902-913.
31. Yang S, Dai P, Liu X, et al. Genetic and phenotypic heterogeneity in Chinese patients with waardenburg syndrome type II. *PLoS ONE*. 2013;8(10):e77149.
32. Spritz RA, Giebel LB, Holmes SA. Dominant-negative and loss of function mutations of the c-kit (mast/stem cell growth factor receptor) proto-oncogene in human piebaldism. *Am J Hum Genet*. 1992;50(2):261-269.
33. Spritz RA, Holmes SA, Ramesar R, Greenberg J, Curtis D, Beighton P. Mutations of the KIT (mast/stem cell growth factor receptor) proto-oncogene account for a continuous range of phenotypes in human piebaldism. *Am J Hum Genet*. 1992;51(5):1058-1065.
34. Spritz RA, Holmes SA, Berg SZ, Nordlund JJ, Fukai K. A recurrent deletion in the KIT (mast/stem cell growth factor receptor) proto-oncogene is a frequent cause of human piebaldism. *Hum Mol Genet*. 1993;2(9):1499-1500.
35. Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism. *Proc Natl Acad Sci U S A*. 1991;88(19):8696-8699.
36. Wasag B, Chmara M, Legius E. Molecular characterization of two novel KIT mutations in patients with piebaldism. *J Dermatol Sci*. 2012;66(1):78-79.

37. Xu X-H, Ma L, Weng L, Xing H. A novel mutation of *KIT* gene results in piebaldism in a Chinese family. *J Eur Acad Dermatol Venereol*. 2016;30(2):336-338.
38. Murakami T, Hosomi N, Oiso N, et al. Analysis of KIT, SCF, and initial screening of SLUG in patients with Piebaldism. *J Invest Dermatol*. 2005;124(3):670-672.
39. Legare JM, Sekhon GS, Laxova R. De novo translocation involving chromosomes 1 and 4 resulting in partial duplication of 4q and partial deletion of 1p. *Am J Med Genet*. 1994;53(3):216-221.
40. Moreno-García M, Sánchez del Pozo J, Cruz-Rojo J, Fernández-Martínez FJ, Perez-Nanclares Leal G. Array-based characterization of an interstitial de-novo deletion of chromosome 4q in a patient with a neuronal migration defect and hypocalcemia plus a literature review. *Clin Dysmorphol*. 2012;21(3):172-176.
41. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. *Arch Dermatol*. 1996;132(10):1167-1170.
42. Cohen J, Shahrokh K, Cohen B. Analysis of 36 cases of blaschkoid dyspigmentation: reading between the lines of Blaschko. *Pediatr Dermatol*. 2014;31(4):471-476.
43. Fujimoto A, Reddy KS, Spinks R. Interstitial deletion of chromosome 4, del(4)(q12q21.1), in a mentally retarded boy with a piebald trait, due to maternal insertion, ins(8;4). *Am J Med Genet*. 1998;75(1):78-81.
44. Slavotinek A, Kingston H. Interstitial deletion of bands 4q12–> q13.1: case report and review of proximal 4q deletions. *J Med Genet*. 1997;34(10):862-865.
45. Jung HJ, Jin SA, Choi SJN, Lee S-C, Yun SJ. A de novo SOX10 mutation in a patient with Waardenburg syndrome type IV. *J Am Acad Dermatol*. 2013;68(6):e177-e178.
46. Jimbow K, Fitzpatrick TB, Szabo G, Hori Y. Congenital circumscribed hypomelanosis: a characterization based on electron microscopic study of tuberous sclerosis, nevus depigmentosus, and piebaldism. *J Invest Dermatol*. 1975;64(1):50-62.
47. Wadhwani M, Gupta Y, Gangwani K. Waardenburg Shah syndrome: a rare case from India. *Oman J Ophthalmol*. 2015;8(1):74.
48. Gupta R, Sharma SB, Mathur P, Agrawal LD. Waardenburg syndrome presenting with constipation since birth. *Indian Pediatr*. 2014;51(12):1013-1014.
49. Arimoto Y, Namba K, Nakano A, Matsunaga T. Chronic constipation recognized as a sign of a SOX10 mutation in a patient with Waardenburg syndrome. *Gene*. 2014;540(2):258-262.
50. de Lorijn F, Kremer LCM, Reitsma JB, Benninga MA. Diagnostic tests in Hirschsprung disease. *J Pediatr Gastroenterol Nutr*. 2006;42(5):496-505.
51. Boehm U, Bouloux P-M, Dattani MT, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol*. 2015;11(9):547-564.
52. Hutson JMHJ, Hutson JM, Grover SR, Oconnell M, Pennell SD. Malformation syndromes associated with disorders of sex development. *Nat Rev Endocrinol*. 2014;10:476-487.
53. Truwit CL, Barkovich AJ, Grumbach MM, Martini JJ. MR imaging of Kallmann syndrome, a genetic disorder of neuronal migration affecting the olfactory and genital systems. *AJNR Am J Neuroradiol*. 1993;14(4):827-838.
54. Zhang Z, Sun X, Wang C, Wang G, Zhao B. Magnetic resonance imaging findings in Kallmann syndrome. *J Comput Assist Tomogr*. 2016;40(1):39-42.
55. Vaaralahti K, Tommiska J, Tillmann V, et al. De novo SOX10 nonsense mutation in a patient with Kallmann syndrome and hearing loss. *Pediatr Res*. 2014;76(1):115-116.
56. Pingault V, Faubert E, Baral V, et al. *SOX10* mutations mimic isolated hearing loss. *Clin Genet*. 2015;88(4):352-359.
57. Izumi Y, Musha I, Suzuki E, et al. Hypogonadotropic hypogonadism in a female patient previously diagnosed as having waardenburg syndrome due to a sox10 mutation. *Endocrine*. 2015;49(2):553-556.
58. Suzuki E, Izumi Y, Chiba Y, et al. Loss-of-function SOX10 mutation in a patient with Kallmann syndrome, hearing loss, and iris hypopigmentation. *Horm Res Paediatr*. 2015;84(3):212-216.
59. Pingault V, Bodereau V, Baral V, et al. Loss-of-function mutations in SOX10 cause kallmann syndrome with deafness. *Am J Hum Genet*. 2013;92(5):707-724.
60. Suzuki N, Mutai H, Miya F, et al. A case report of reversible generalized seizures in a patient with Waardenburg syndrome associated with a novel nonsense mutation in the penultimate exon of SOX10. *BMC Pediatr*. 2018;18(1):171.
61. Shin S-J, Sul Y, Kim JH, et al. Clinical, endocrinological, and molecular characterization of Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism: a single center experience. *Ann Pediatr Endocrinol Metab*. 2015;20(1):27.
62. Topaloglu AK, Kotan LD. Genetics of hypogonadotropic hypogonadism. *Endocr Dev*. 2016;29:36-49.
63. Maione L, Brailly-Tabard S, Nevoux J, Bouligand J, Young J. Reversal of congenital hypogonadotropic hypogonadism in a man with Kallmann syndrome due to *SOX10* mutation. *Clin Endocrinol (Oxf)*. 2016;85(6):988-989.
64. Bademci G, Cengiz FB, Foster J II, et al. Variations in multiple syndromic deafness genes mimic non-syndromic hearing loss. *Sci Rep*. 2016;6(1):31622.
65. Elmaleh-Berges M, Baumann C, Noel-Petroff N, et al. Spectrum of temporal bone abnormalities in patients with waardenburg syndrome and SOX10 mutations. *Am J Neuroradiol*. 2013;34(6):1257-1263.
66. Jalilian N, Tabatabaiefar MA, Alimadadi H, Noori-Daloii MR. SOX10 mutation causes Waardenburg syndrome associated with distinctive phenotypic features in an Iranian family: a clue for phenotype-directed genetic analysis. *Int J Pediatr Otorhinolaryngol*. 2017;96:122-126.
67. Bondurand N, Dastot-Le Moal F, Stanchina L, et al. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. *Am J Hum Genet*. 2007;81(6):1169-1185.
68. Maione L, Cantone E, Nettore IC, et al. Flavor perception test: evaluation in patients with Kallmann syndrome. *Endocrine*. 2016;52(2):236-243.
69. Hart J, Miriyala K. Neural tube defects in Waardenburg syndrome: a case report and review of the literature. *Am J Med Genet Part A*. 2017;173(9):2472-2477.
70. Final Update Summary: Folic Acid to Prevent Neural Tube Defects: Preventive Medication. U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/folic-acid-to-prevent-neural-tube-defects-preventive-medication. Published 2015. Accessed May 28, 2017.
71. Ramien ML, Ondrejchak S, Gendron R, et al. Quality of life in pediatric patients before and after cosmetic camouflage of visible skin conditions. *J Am Acad Dermatol*. 2014;71(5):935-940.
72. Levy LL, Emer JJ. Emotional benefit of cosmetic camouflage in the treatment of facial skin conditions: personal experience and review. *Clin Cosmet Investig Dermatol*. 2012;5:173-182.
73. Suga Y, Ikejima A, Matsuba S, Ogawa H. Medical pearl: DHA application for camouflaging segmental vitiligo and piebald lesions. *J Am Acad Dermatol*. 2002;47(3):436-438.
74. Richards KA, Fukai K, Oiso N, Paller AS. A novel KIT mutation results in piebaldism with progressive depigmentation. *J Am Acad Dermatol*. 2001;44(2):288-292.
75. Maderal AD, Kirsner RS. Use of epidermal grafting for treatment of depigmented skin in piebaldism. *Dermatol Surg*. 2017;43(1):159-160.

76. Garg T, Khaitan BK, Manchanda Y. Autologous punch grafting for repigmentation in piebaldism. *J Dermatol*. 2003;30(11):849-850.
77. Komen L, Vrijman C, Tjin EPM, et al. Autologous cell suspension transplantation using a cell extraction device in segmental vitiligo and piebaldism patients: a randomized controlled pilot study. *J Am Acad Dermatol*. 2015;73(1):170-172.
78. Njoo MD, Nieuweboer-Krobotova L, Westerhof W. Repigmentation of leucodermic defects in piebaldism by dermabrasion and thin split-thickness skin grafting in combination with minigrafting. *Br J Dermatol*. 1998;139(5):829-833.
79. Olsson MJ, Juhlin L. Long-term follow-up of leucoderma patients treated with transplants of autologous cultured melanocytes, ultrathin epidermal sheets and basal cell layer suspension. *Br J Dermatol*. 2002;147(5):893-904.
80. Van Geel N, Wallaeys E, Goh BK, De Mil M, Lambert J. Long-term results of noncultured epidermal cellular grafting in vitiligo, halo naevi, piebaldism and naevus depigmentosus. *Br J Dermatol*. 2010;163(6):1186-1193.
81. Arase N, Wataya-Kaneda M, Oiso N, et al. Repigmentation of leukoderma in a piebald patient associated with a novel c-KIT gene mutation, G592E, of the tyrosine kinase domain. *J Dermatol Sci*. 2011;64(2):147-149.
82. Lommerts JE, Meesters AA, Komen L, et al. Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomized controlled trial comparing full surface and fractional CO_2 laser recipient-site preparations. *Br J Dermatol*. 2017;177(5):1293-1298.
83. Guerra L, Primavera G, Raskovic D, et al. Permanent repigmentation of piebaldism by erbium:YAG laser and autologous cultured epidermis. *Br J Dermatol*. 2004;150(4):715-721.
84. Komen L, Vrijman C, Prinsen CAC, van der Veen JPW, Luiten RM, Wolkerstorfer A. Optimising size and depth of punch grafts in autologous transplantation of vitiligo and piebaldism: a randomised controlled trial. *J Dermatolog Treat*. 2017;28(1):86-91.
85. Frampton S, Ismail-Koch H, Mitchell T. How safe is diathermy in patients with cochlear implants? *Ann R Coll Surg Engl*. 2012;94(8):585-587.
86. Harlor ADB, Bower C. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics*. 2009;124(4):1252-1263.
87. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120(4):898-921.
88. Cullen RD, Zdanski C, Roush P, et al. Cochlear implants in Waardenburg syndrome. *Laryngoscope*. 2006;116(7):1273-1275.
89. de Sousa Andrade SM, Monteiro ART, Martins JHF, et al. Cochlear implant rehabilitation outcomes in Waardenburg syndrome children. *Int J Pediatr Otorhinolaryngol*. 2012;76(9):1375-1378.
90. Kontorinis G, Lenarz T, Giourgas A, Durisin M, Lesinski-Schiedat A. Outcomes and special considerations of Cochlear implantation in Waardenburg syndrome. *Otol Neurotol*. 2011;32(6):951-955.
91. Deka RC, Sikka K, Chaturvedy G, et al. Cochlear implantation in Waardenburg syndrome: the Indian scenario. *Acta Otolaryngol*. 2010;130(10):1097-1100.
92. Daneshi A, Hassanzadeh S, Farhadi M. Cochlear implantation in children with Waardenburg syndrome. *J Laryngol Otol*. 2005;119(9):719-723.
93. van Nierop JWI, Snabel RR, Langereis M, et al. Paediatric cochlear implantation in patients with Waardenburg syndrome. *Audiol Neurotol*. 2016;21(3):187-194.
94. Nuorti JP, Whitney CG, Centers for Disease Control and Prevention (CDC). Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-11):1-18.
95. Reefhuis J, Honein MA, Whitney CG, et al. Risk of bacterial meningitis in children with cochlear implants. *N Engl J Med*. 2003;349(5):435-445.
96. Pingault V, Girard M, Bondurand N, et al. SOX10 mutations in chronic intestinal pseudo-obstruction suggest a complex physiopathological mechanism. *Hum Genet*. 2002;111(2):198-206.
97. Baral V, Chaoui A, Watanabe Y, et al. Screening of MITF and SOX10 regulatory regions in waardenburg syndrome type 2. Janecke AR, ed. *PLoS ONE*. 2012;7(7):e41927.
98. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat*. 2010;31(4):391-406.
99. Bocángel 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.
100. Kawakami A, Fisher DE. The master role of microphthalmia-associated transcription factor in melanocyte and melanoma biology. *Lab Invest*. 2017;97(6):649-656.
101. Levy C, Khaled M, Fisher DE. MITF: master regulator of melanocyte development and melanoma oncogene. *Trends Mol Med*. 2006;12(9):406-414.
102. Lauss M, Haq R, Cirenajwis H, et al. Genome-wide DNA methylation analysis in melanoma reveals the importance of CpG methylation in MITF regulation. *J Invest Dermatol*. 2015;135(7):1820-1828.
103. Wang X-P, Liu Y-L, Mei L-Y, et al. Wnt signaling pathway involvement in genotypic and phenotypic variations in Waardenburg syndrome type 2 with MITF mutations. *J Hum Genet*. 2018;63(5):639-646.
104. Amiel J, Watkin PM, Tassabehji M, Read AP, Winter RM. Mutation of the MITF gene in albinism-deafness syndrome (Tietz syndrome). *Clin Dysmorphol*. 1998;7(1):17-20.
105. Smith SD, Kelley PM, Kenyon JB, Hoover D. Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF. *J Med Genet*. 2000;37(6):446-448.
106. George A, Zand DJ, Hufnagel RB, et al. Biallelic mutations in MITF cause coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness. *Am J Human Genet*. 2016;99(6):1388-1394. Human Genetic Variation Database.
107. Human Genetic Variation Database. http://www.hgvd.genome.med.kyoto-u.ac.jp/index.html. Accessed September 1, 2018.
108. Kervestin S, Jacobson A. NMD: a multifaceted response to premature translational termination. *Nat Rev Mol Cell Biol*. 2012;13(11):700-712.
109. Bogdanova-Mihaylova P, Alexander MD, Murphy RPJ, Murphy SM. Waardenburg syndrome: a rare cause of inherited neuropathy due to SOX10 mutation. *J Peripher Nerv Syst*. 2017;22(3):219-223.
110. Liang F, Zhao M, Fan L, et al. Identification of a de novo mutation of SOX10 in a Chinese patient with Waardenburg syndrome type IV. *Int J Pediatr Otorhinolaryngol*. 2016;91:67-71.
111. Wang X, Zhu Y, Shen N, et al. A de novo deletion mutation in SOX10 in a Chinese family with Waardenburg syndrome type 4. *Sci Rep*. 2017;7:41513.
112. Wenzhi H, Ruijin W, Jieliang L, et al. Heterozygous deletion at the SOX10 gene locus in two patients from a Chinese family with Waardenburg syndrome type II. *Int J Pediatr Otorhinolaryngol*. 2015;79(10):1718-1721.
113. Watanabe A, Takeda K, Ploplis B, Tachibana M. Epistatic relationship between Waardenburg syndrome genes MITF and PAX3. *Nat Genet*. 1998;18(3):283-286.
114. Zhang H, Feng J, Chen H, Li J, Luo H, Feng Y. Analysis of nuclear localization and signal function of MITF protein predisposing to Warrdenburg syndrome. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2015;32(6):805-809.
115. Sánchez-Martín M, Rodríguez-García A, Pérez-Losada J, Sagrera A, Read AP, Sánchez-García I. SLUG (SNAI2) deletions in patients with Waardenburg disease. *Hum Mol Genet*. 2002;11(25):3231-3236.

116. Kuphal S, Bosserhoff AK. E-cadherin cell–cell communication in melanogenesis and during development of malignant melanoma. *Arch Biochem Biophys*. 2012;524(1):43-47.
117. Carlson BM, ed. In: *Human Embryology and Developmental Biology*. 5th ed. Philadelphia: Saunders; 2013:254-293.
118. Kim JE, Leung E, Baguley BC, Finlay GJ. Heterogeneity of expression of epithelial-mesenchymal transition markers in melanocytes and melanoma cell lines. *Front Genet*. 2013;4:97.
119. Wilson YM, Richards KL, Ford-Perriss ML, Panthier J-J, Murphy M. Neural crest cell lineage segregation in the mouse neural tube. *Development*. 2004;131(24):6153-6162.
120. Pérez-Losada J, Sánchez-Martín M, Rodríguez-García A, et al. Zinc-finger transcription factor Slug contributes to the function of the stem cell factor c-kit signaling pathway. *Blood*. 2002;100(4):1274-1286.
121. Zhang Z, Zhu P, Zhou Y, et al. A novel slug-containing negative-feedback loop regulates SCF/c-Kit-mediated hematopoietic stem cell self-renewal. *Leukemia*. 2017;31(2):403-413.
122. Yang Y, Zhao R, He X, et al. *SNAI2* mutation causes human piebaldism. *Am J Med Genet Part A*. 2014;164(3):855-857.
123. Sánchez-Martín M, Pérez-Losada J, Rodríguez-García A, et al. Deletion of the SLUG (SNAI2) gene results in human piebaldism. *Am J Med Genet A*. 2003;122A(2):125-132.
124. Steingrímsson E, Copeland NG, Jenkins NA. Melanocyte stem cell maintenance and hair graying. *Cell*. 2005;121(1):9-12.
125. Nishimura EK, Granter SR, Fisher DE. Mechanisms of hair graying: incomplete melanocyte stem cell maintenance in the niche. *Science*. 2005;307(5710):720-724.
126. Veis DJ, Sorenson CM, Shutter JR, Korsmeyer SJ. Bcl-2-deficient mice demonstrate fulminant lymphoid apoptosis, polycystic kidneys, and hypopigmented hair. *Cell*. 1993;75(2):229-240.
127. Loercher AE, Tank EMH, Delston RB, Harbour JW. MITF links differentiation with cell cycle arrest in melanocytes by transcriptional activation of INK4A. *J Cell Biol*. 2005;168(1):35-40.
128. Hofstra RMW, Osinga J, Tan-Sindhunata G, et al. A homozygous mutation in the endothelin-3 gene associated with a combined Waardenburg type 2 and Hirschsprung phenotype (Shah-Waardenburg syndrome). *Nat Genet*. 1996;12(4):445-447.
129. Doubaj Y, Pingault V, Elalaoui SC, et al. A novel mutation in the endothelin B receptor gene in a moroccan family with Shah-Waardenburg syndrome. *Mol Syndromol*. 2015;6(1):44-49.
130. Sergi C, Caluseriu O, McColl H, Eisenstat DD. Hirschsprung's disease: clinical dysmorphology, genes, micro-RNAs and future perspectives. *Pediatr Res*. 2016;81(1–2):177-191.
131. Kerkeni E, Boubaker S, Sfar S, et al. Molecular characterization of piebaldism in a Tunisian family. *Pathol Biol*. 2015;63(3):113-116.
132. Black FO, Pesznecker SC, Allen K, Gianna C. A vestibular phenotype for Waardenburg syndrome? *Otol Neurotol*. 2001;22(2):188-194.
133. Hoth CF, Milunsky A, Lipsky N, Sheffer R, Clarren SK, Baldwin CT. Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). *Am J Hum Genet*. 1993;52(3):455-462.
134. Wollnik B, Tukel T, Uyguner O, et al. Homozygous and heterozygous inheritance ofPAX3 mutations causes different types of Waardenburg syndrome. *Am J Med Genet*. 2003;122A(1):42-45.
135. Sun L, Li X, Shi J, et al. Molecular etiology and genotype-phenotype correlation of Chinese Han deaf patients with type I and type II Waardenburg Syndrome. *Sci Rep*. 2016;6(1):35498.
136. Chen H, Jiang L, Xie Z, et al. Novel mutations of PAX3, MITF, and SOX10 genes in Chinese patients with type I or type II Waardenburg syndrome. *Biochem Biophys Res Commun*. 2010;397(1):70-74.
137. Okamura K, Oiso N, Tamiya G, et al. Waardenburg syndrome type IIE in a Japanese patient caused by a novel missense mutation in the SOX10 gene. *J Dermatol*. 2015;42(12):1211-1212.
138. Zhang H, Chen H, Luo H, et al. Functional analysis of Waardenburg syndrome-associated PAX3 and SOX10 mutations: report of a dominant-negative SOX10 mutation in Waardenburg syndrome type II. *Hum Genet*. 2012;131(3):491-503.
139. Xu GY, Hao QQ, Zhong LL, et al. SOX10 mutation is relevant to inner ear malformation in patients with Waardenburg syndrome. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2016;51(11):832-837.
140. Issa S, Bondurand N, Faubert E, et al. *EDNRB* mutations cause Waardenburg syndrome type II in the heterozygous state. *Hum Mutat*. 2017;38(5):581-593.
141. Kilsby AJ, Cruwys M, Kukendrajah C, et al. Homozygosity for piebaldism with a proven KIT mutation resulting in depigmentation of the skin and hair, deafness, developmental delay and autism spectrum disorder. *Clin Dysmorphol*. 2013;22(2):64-67.
142. Zazo Seco C, Serrão de Castro L, van Nierop JW, et al. Allelic mutations of KITLG, encoding KIT ligand, cause asymmetric and unilateral hearing loss and waardenburg syndrome type 2. *Am J Hum Genet*. 2015;97(5):647-660.
143. Ogawa Y, Kono M, Akiyama M. Pigmented macules in Waardenburg syndrome type 2 due to KITLG mutation. *Pigment Cell Melanoma Res*. 2017;30(5):501-504.
144. Jan IA, Stroedter L, Haq A, Din Z. Association of Shah-Waardenburgh syndrome: a review of 6 cases. *J Pediatr Surg*. 2008;43(4):744-747.
145. Moore SW. Chromosomal and related Mendelian Syndromes associated with Hirschsprung's disease. *Pediatr Surg Int*. 2012;28(11):1045-1058.
146. Leechawengwongs E, Tison BE, Gopalakrishna GS, et al. Does short bowel syndrome increase the risk of food allergy and eosinophilic gastrointestinal disease? Observations in Shah-Waardenburg syndrome. *J Allergy Clin Immunol*. 2013;131(1):251-255.
147. Inoue K, Shilo K, Boerkoel CF, et al. Congenital hypomyelinating neuropathy, central dysmyelination, and Waardenburg-Hirschsprung disease: phenotypes linked bySOX10 mutation. *Ann Neurol*. 2002;52(6):836-842.
148. Unzicker A, Pingault V, Meyer T, Rauthe S, Schütz A, Kunzmann S. A novel SOX10 mutation in a patient with PCWH who developed hypoxic-ischemic encephalopathy after *E. coli* sepsis. *Eur J Pediatr*. 2011;170(11):1475-1480.
149. Song J, Feng Y, Acke FR, Coucke P, Vleminckx K, Dhooge IJ. Hearing loss in Waardenburg syndrome: a systematic review. *Clin Genet*. 2016;89(4):416-425.
150. Kujat A, Veith V-P, Faber R, Froster UG. Prenatal diagnosis and genetic counseling in a case of Spina Bifida in a family with Waardenburg syndrome type I. *Fetal Diagn Ther*. 2006;22(2):155-158.
151. Lemay P, Guyot M-C, Tremblay É, et al. Loss-of-function de novo mutations play an important role in severe human neural tube defects. *J Med Genet*. 2015;52(7):493-497.
152. Yoshida Y, Doi R, Adachi K, Nanba E, Kodani I, Ryoke K. A novel PAX3 mutation in a Japanese boy with Waardenburg syndrome type 1. *Hum Genome Var*. 2016;3:16005.
153. Tasdemir S, Erdem HB, Sahin I, Kara M, Tatar A. Waardenburg syndrome type 1 and a rare finding of anal atresia. *Genet Couns*. 2015;26(4):467-470.
154. Itty S, Richter ER, McCannel TA. Choroidal melanoma in a patient with waardenburg syndrome. *Retin Cases Brief Rep*. 2015;9(4):1.
155. Webb KM, Smith AJ, Dansby LM, Diskin CJ. Waardenburg syndrome with familial unilateral renal agenesis: a new syndrome variant? *Ther Apher Dial*. 2015;19(3):296-298.
156. Vichare N, Bhargava N. Waardenburg syndrome: a rare case with bilateral congenital cataract: an unusual entity. *Med J Armed Forces India*. 2013;69(2):172-174.
157. Franz T. Defective ensheathment of motoric nerves in the splotch mutant mouse. *Acta Anat (Basel)*. 1990;138(3):246-253.
158. Franz T. Persistent truncus arteriosus in the Splotch mutant mouse. *Anat Embryol (Berl)*. 1989;180(5):457-464.
159. Zlotogora J, Lerer I, Bar-David S, Ergaz Z, Abeliovich D. Homozygosity for Waardenburg syndrome. *Am J Hum Genet*. 1995;56(5):1173-1178.

160. Wang D, Ren GF, Zhang HZ, Yi CY, Peng ZJ. A de novo 2q35-q36.1 deletion incorporating IHH in a Chinese boy (47,XYY) with syndactyly, type III Waardenburg syndrome, and congenital heart disease. *Genet Mol Res*. 2016;15(4):1-7.
161. Li C, Chen R, Fan X, et al. EPHA4 haploinsufficiency is responsible for the short stature of a patient with 2q35-q36.2 deletion and Waardenburg syndrome. *BMC Med Genet*. 2015;16(1):23.
162. Gross A, Kunze J, Maier RF, Stoltenburg-Didinger G, Grimmer I, Obladen M. Autosomal-recessive neural crest syndrome with albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness: ABCD syndrome. *Am J Med Genet*. 1995;56(3):322-326.
163. Verheij JBGM, Kunze J, Osinga J, van Essen AJ, Hofstra RMW. ABCD syndrome is caused by a homozygous mutation in the EDNRB gene. *Am J Med Genet*. 2002;108(3):223-225.
164. Siomou E, Manolakos E, Petersen M, et al. A 725 kb deletion at 22q13.1 chromosomal region including SOX10 gene in a boy with a neurologic variant of Waardenburg syndrome type 2. *Eur J Med Genet*. 2012;55(11):641-645.
165. Pingault V, Pierre-Louis L, Chaoui A, et al. Phenotypic similarities and differences in patients with a p.Met112Ile mutation in *SOX10*. *Am J Med Genet A*. 2014;164(9):2344-2350.
166. Oshimo T, Fukai K, Abe Y, et al. Pediatric case report: clinical profile of a patient with PCWH with p.Q377X nonsense mutation in the *SOX10* gene. *J Dermatol*. 2012;39(12):1022-1025.
167. Izumi K, Kohta T, Kimura Y, et al. Tietz syndrome: unique phenotype specific to mutations of MITF nuclear localization signal. *Clin Genet*. 2008;74(1):93-95.
168. Reed WB, Stone VM, Boder E, Ziprkowski L. Pigmentary disorders in association with congenital deafness. *Arch Dermatol*. 1967;95(2):176-186.
169. Picardo M, Dell'Anna ML, Ezzedine K, et al. Vitiligo. *Nat Rev Dis Primers*. 2015;1:15011.
170. Taïeb A, Picardo M. Clinical practice. Vitiligo. *N Engl J Med*. 2009;360(2):160-169.
171. Ruocco E, Baroni A, Donnarumma G, Ruocco V. Diagnostic procedures in dermatology. *Clin Dermatol*. 2011;29(5):548-556.
172. Kim SK, Kang HY, Lee ES, Kim YC. Clinical and histopathologic characteristics of nevus depigmentosus. *J Am Acad Dermatol*. 2006;55(3):423-428.
173. Hann S-K, Park Y-K, Chun WH. Clinical features of vitiligo. *Clin Dermatol*. 1997;15:891-897.
174. Gupta S, Goel A. Letter to the editor: nevus depigmentosus needs transplant of epidermal sheets. *Dermatol Surg*. 2005;31(12):1746-1747.
175. Kim DY, Park Y-K, Hann S-K. Recurrence of nevus depigmentosus after an autologous epidermal graft. *J Am Acad Dermatol*. 2008;58(3):527-529.
176. Mulekar SV, Al Issa A, Al Eisa A. Nevus depigmentosus treated by melanocyte-keratinocyte transplantation. *J Cutan Aesthet Surg*. 2011;4(1):29-32.
177. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med*. 2006;355(13):1345-1356.
178. Kromann AB, Ousager LB, Ali IKM, Aydemir N, Bygum A. Pigmentary mosaicism: a review of original literature and recommendations for future handling. *Orphanet J Rare Dis*. 2018;13(1):39.
179. Mavropoulos JC, Cohen BA. Disorders of Pigmentation In: *Pediatric Dermatology*, 4th edn, Elsevier Inc.; 2013:148-168.
180. Ruiz-Maldonado R. Hypomelanotic conditions of the newborn and infant. *Dermatol Clin*. 2007;25(3):373-382.
181. Lee HS, Chun YS, Hann SK. Nevus depigmentosus: clinical features and histopathologic characteristics in 67 patients. *J Am Acad Dermatol*. 1999;40(1):21-26.
182. Jindal R, Jain A, Gupta A, Shirazi N. Ash-leaf spots or naevus depigmentosus: a diagnostic challenge. *BMJ Case Rep*. 2013;2013:bcr2012007008.
183. Thappa D, Sori T, Nath A, Jaisankar T. Hypopigmentary disorders in children in South India. *Indian J Dermatol*. 2011;56(5):546.
184. Vanderhooft SL, Francis JS, Pagon RA, Smith LT, Sybert VP. Prevalence of hypopigmented macules in a healthy population. *J Pediatr*. 1996;129(3):355-361.
185. Boudjadi S, Chatterjee B, Sun W, Vemu P, Barr FG. The expression and function of PAX3 in development and disease. *Gene*. 2018;666:145-157.
186. Mollaaghababa R, Pavan WJ. The importance of having your SOX on: role of SOX10 in the development of neural crest-derived melanocytes and glia. *Oncogene*. 2003;22(20):3024-3034.
187. Maier EC, Saxena A, Alsina B, Bronner ME, Whitfield TT. Sensational placodes: neurogenesis in the otic and olfactory systems. *Dev Biol*. 2014;389(1):50-67.
188. Barraud P, St John JA, Stolt CC, Wegner M, Baker CVH. Olfactory ensheathing glia are required for embryonic olfactory axon targeting and the migration of gonadotropin-releasing hormone neurons. *Biol Open*. 2013;2(7):750-759.
189. Kim H, Ankamreddy H, Lee DJ, et al. Pax3 function is required specifically for inner ear structures with melanogenic fates. *Biochem Biophys Res Commun*. 2014;445(3):608-614.
190. Forni PE, Wray S. GnRH, anosmia and hypogonadotropic hypogonadism—Where are we? *Front Neuroendocrinol*. 2015;36:165-177.

How to cite this article: Saleem MD. Biology of human melanocyte development, Piebaldism, and Waardenburg syndrome. *Pediatr Dermatol*. 2019;36:72-84. https://doi.org/10.1111/pde.13713