Pigment Genodermatoses Affecting Melanocyte Development and Migration from the Neural Crest: Piebaldism, Waardenburg Syndrome and Cross-McKusick-Breen Syndrome

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Abstract

Piebaldism, Waardenburg syndrome and Cross-McKusick-Breen syndrome are rare disorders characterized by congenital skin and hair hypopigmentation. Piebaldism is inherited in an autosomal dominant pattern and Waardenburg syndrome is mostly transmitted in an autosomal dominant manner. These diseases are caused by abnormal migration of melanoblasts from the neuroectoderm into the skin. Cross-McKusick-Breen syndrome is an autosomal recessive disorder in which the epidermal melanocyte numbers are normal, but most melanosomes are in stage II or III and are probably characterized by defective melanosomal transfer. This publication describes the clinical and genetic characteristics of the three selected genodermatoses. Although rare and phenotypically diverse, the study of these diseases has yielded significant knowledge on the genes that regulate the migration of melanocytes and the mechanisms that control skin, hair and eye pigmentation.

Keywords: Piebaldism; Waardenburg syndrome; Cross-McKusick-Breen syndrome

Abbreviations: CMBS: Cross–Mckusick–Breen Syndrome; EDN3: Endothelin-3; EDNRB: Endothelin B Receptor; HSCR: Hirschsprung Disease; KIT: Receptor Tyrosine Kinase 2; KITLG: KIT Ligand, Stem Cell Factor; MC1R: Melanocortin 1 Receptor; MITF: Microphthalmia-Associated Transcription Factor; OCA: Oculocutaneous Albinism; OCHS: Oculocerebral Hypopigmentation Syndrome; PAX-3: Paired Box 3; SNAI2: Nail Family Zinc Finger 2; SOX10: Sex Determining Region Y-Box 10; TYR: Tyrosinase; WS: Waardenburg Syndrome; WS1: Waardenburg Syndrome Type I; WS2 : Waardenburg Syndrome Type II; WS3: Waardenburg Syndrome Type III or Klein-Waardenburg Syndrome; WS4: Waardenburg Syndrome Type IV or Shah-Waardenburg Syndrome

Introduction

The pigmentation of the skin is, except in rare pathological instances, the result of three pigments or chromophores: melanin, a brown/black (eumelanin) or red/yellow polymer (pheomelanin) produced by melanocytes; hemoglobin in red blood cells in the superficial vasculature; and dietary carotenoids [1]. Melanin, the most important, is formed from tyrosine, via the action of tyrosinase in the lysosome-related organelles of melanocytes, called melanosomes. Melanosomes are dendritic cells, arising from the neural crest during embryonic development and located in the basal layer of the epidermis. The migration of melanoblasts from the neural crest are controlled by genes, such as c-KIT receptor tyrosine kinase and the transcription factors PAX-3 and MITF. The melanosomes are transferred from a melanocyte to a group of 36 keratinocytes called the epidermal melanin unit, to which they provide melanin.

Interest in the genetics of human pigmentation is longstanding. Variation in human pigmented form - of skin, hair, and eyes - is one of the most striking polymorphic human traits [2]. More than 150 genes have now been identified that affect pigmentation of the skin, hair and/or eyes such as TYR, MC1R, OCA. The availability of large-scale DNA analysis and genome-wide scans, together with our existing knowledge of the genes involved in pigmentation, have contributed to the interpretation of the mechanism of skin pigmentation [2,3].

Disorders of pigmentation can result from migration abnormalities of melanocytes from the neural crest to the skin during embryogenesis. In addition, impairment of melanosomal transfer to the surrounding keratinocytes, an alteration in melanin synthesis and a defective degradation or removal of melanin may lead to abnormal skin pigmentation. Immunologic or toxic mediated destructions of melanocytes can also cause pigmentation abnormalities. Disorders of pigmentation are classified in hypo- or hyperpigmentation which can occur as a genetic or acquired disease. They can manifest locally or diffusely [4,5].

Piebaldism, Waardenburg syndrome and Cross–McKusick–Breen syndrome are rare disorders characterized by congenital skin and hair hypopigmentation. Piebaldism is inherited in an autosomal dominant pattern and Waardenburg syndrome is mostly transmitted in an autosomal dominant manner. These diseases are caused by abnormal migration of melanoblasts from the neuroectoderm into the skin. Cross-McKusick-Breen syndrome is an autosomal recessive disorder in which the epidermal melanocyte numbers are normal, but most melanosomes are in stage II or III and are probably characterized by defective melanosomal transfer.

Piebaldism

Definition

Piebaldism is a rare, autosomal dominant disorder. The incidence of piebaldism is estimated to be less than 1:20000. Both males and females are equally affected, and no race is spared [6]. The disorder is characterized by the congenital absence of melanocytes in the affected
areas of the hair and skin. This striking phenotype of depigmented patches of skin and hair has been observed throughout history, with the first descriptions dating to early Egyptian, Greek and Roman writings. Generation after generation demonstrated a distinctive predictable familial mark—a white forelock. Families have sometimes been known for this mark of distinction, carrying such surnames as Whitlock, Horlick, and Blaylock. The word "piebald" has been attributed to a combination of the "pie" in the magpie (a bird of black and white plumage) and the "bald" of the bald eagle (Haliaeetus leucocephalus) (which has a white feathered head) [7].

Clinical features

The lesions are present at birth. The depigmented lesions are static and typically occur on the anterior and posterior trunk, mid-upper arm to wrist, mid-thigh to mid-calf, and shins. A characteristic feature of piebaldism is the presence of hyperpigmented macules within the areas lacking pigmentation and also on normally pigmented skin (Figure 1). The depigmented lesions may repigment spontaneously, or after injury. The presence of lesions since birth, the stability of lesions, and the presence of pigmented patches within lesions differentiate piebaldism from vitiligo. The white forelock is a triangular or diamond-shaped midline white macule on the frontal scalp or forehead (Figure 2). Scapul poliosis (white forelock) is present in 80% to 90% of patients. All the hairs of the forelock are white and the underlying skin is also amelanotic. Poliosis of the eyebrows and eyelashes is common [8,9]. Melanocytes are absent or considerably reduced in depigmented patches histologically and ultrastructurally. They are normal in number in the normally pigmented areas.

Genetics/pathogenesis

Piebaldism is caused by mutations in the KIT gene (receptor tyrosine kinase). This gene, located on chromosome 4q12, is involved in the differentiation and migration of melanoblasts from the neural crest during the embryonic life. The receptor KIT is a member of the type III group of transmembrane receptor tyrosine kinase and is composed of an amino-terminal extracellular ligand-binding domain, a single transmembrane domain, and a cytoplasmic region. The binding of KITLG (KIT ligand, stem cell factor) to the extracellular domain leads to receptor dimerization, intracellular autophosphorylation and tyrosine kinase activation. The binding of KITLG to KIT regulates the migration of melanocytes, cell proliferation, differentiation, survival, melanogenesis and melanosome transfer [10].

Clinical manifestations and phenotypic severity of piebaldism strongly correlate with the site of the mutation within the KIT gene. Dominant negative missense mutations of the intracellular tyrosine kinase domain appear to yield the most severe phenotypes, while mutations in the amino terminal extracellular ligand-binding domain result in haploinsufficiency and are associated with the mildest forms of piebaldism. Intermediate phenotypes are seen with mutations near the transmembrane region. The classic type of static piebaldism is due to c-kit gene mutations in the vicinity of codon 620 (Val620Ala, 1859T>C) [6,9].

After identification of a missense mutation in the KIT gene in a large family, 32 missense mutations, 17 deletions, 4 insertions, 7 nucleotide splice-site mutations, 2 nonsense mutations and 1 pericentric chromosomal inversion have been identified in the KIT gene or in the chromosomal region of the KIT gene. These genetic studies provide further evidence that the clinical diversity of piebaldism depends on the site and the type of mutation in the KIT gene [10].

Association with other disorders

Piebaldism may be associated with other disorders. Rare associations have been reported with Hirschsprung’s disease or aganglionic megacolon, supporting evidence of a network of interacting genes and proteins that regulate melanocytes and the enteric plexus neurons during their development at the time of embryogenesis. Neurofibromatosis Type I has been reportedly associated with piebaldism in a few cases. A piebald patient with congenital dyserythropoietic anemia Type II (HEMPAS) and a patient with Diamond-Blackfan anemia have been also reported. Grover’s Disease or transient acantholytic dermatosis limited to the depigmented macules in a patient with piebaldism has been described [6,9,11].

Treatment

Cosmetic camouflage or skin dyes may be helpful for some patients. Photoprotective preparations should be prescribed to protect the amelanotic areas from burning with sun exposure. The white patches in piebaldism are stable. Surgical treatment with autologous transplantation techniques (minigrafting, suction blister epidermal grafting, grafting of cultured autologous melanocytes, and grafting of noncultured epidermal cell suspensions) can be used to improve the appearance of lesions [8]. Treatment with a combination of dermabrasion and grafting or a combination of Erbium:YAG laser.
surgery for disepithelialization and autologous cultured epidermal grafting on the recipient bed have been reported [11,12].

Waardenburg Syndrome (WS)

Definition

Waardenburg Syndrome (WS) is a rare auditory-pigmentary disorder caused by physical absence of melanocytes from the skin, hair, eyes, or the stria vascularis of the cochlea. Four WS types have been described on clinical grounds (Table 1).

Clinical features

On 14 December 1947 the Dutch ophthalmologist and geneticist Waardenburg presented a deaf-mute man with “dystopia punctorum lacrimarum, blepharophimosis and partial iris atrophy” at a meeting of the Dutch Ophthalmological Society. The patient had blue eyes but was bald and Waardenburg did not at the time make the connection between hearing loss, white forelock, unusual eye colour, and dystopia canthorum. He reported a mention of twins with the same eye abnormality who were “coincidentally” also deaf-mute. Realising that coincidences were multiplying, Waardenburg was prompted to undertake a systematic search among 1050 inmates of five Dutch institutions for the deaf. Waardenburg's results, published in an extensive paper in the American Journal of Human Genetics in 1951, defined the syndrome now named type I Waardenburg syndrome (WS1).

He described a new syndrome, consisting of 1. lateral displacement of the medial canthi and lacrimal points, 2. a hyperplastic, broad, high nasal root, 3. hyperplasia of the medial portions of the eyebrows, 4. partial or total heterochromia iridum, 5. congenital deafness or partial (unilateral) deafness, and 6. circumscribed albinism of the frontal head hair (white forelock) (Figure 3). Among 840 deaf-mutes in five Dutch institutes for the deaf, 12 cases of the new syndrome were discovered. He characterized the syndrome as autosomal dominant with very high penetrance of dystopia but reduced penetrance of all other features.

Waardenburg estimated the prevalence of his syndrome to be 1/42000 of the population and 1.43% of the congenitally deaf. Five out of 16 probands having the syndrome were apparently sporadic cases [13,14]. On their data, Zaman et al., estimated a prevalence of 0.119 - 0.208 per 1,000 which was higher than the previously reported prevalence [15]. Swiss ophthalmologist David Klein also made contributions towards the understanding of the syndrome. WS2 was identified in 1992, the Waardenburg Syndrome Consortium proposed the diagnostic criteria for Waardenburg syndrome type I (WS1). Individuals should be considered to have WS1 if they had two major, or one major and two minor criteria from the list in Table 2 [16]. In 1995, Liu, Newton and Read used the same list to define WS2. Individuals with two major features and who did not have dystopia canthorum were considered to have WS2 [17]. Other types of WS have been identified, but they are less common (Table 1). Type I is characterized by dystopia canthorum, deafness in 60% of patients, and the distinctive facial features of WS, mainly a high nasal bridge, synophrys, and hypoplasia of the alae nasi (Figure 3). In type II there is no dystopia canthorum and over 80% of patients have deafness, while 47% had heterochromia iridum. Type III or Klein-Waardenburg syndrome is a severe form of type I presenting with skeletal abnormalities. Type IV or Shah-Waardenburg syndrome is characterized by the association of WS and Hirschsprung disease [18,19].

Genetics/Pathogenesis

This syndrome is usually inherited in an autosomal dominant pattern. A small percentage of cases result from new mutations in the gene, these cases occur in people with no history of the disorder in their family. Some cases of type II and type IV WS appear to have an autosomal recessive pattern of inheritance.

Specific genes, including *PAX3, MITF, SNAI2, EDNS, EDNRB* and *SOX10*, have been related to WS, with each of these genes playing a significant role in differentiating the numerous manifestations of WS [20] (Table 1).

| Type          | Clinical features                          | Gene mutated (chromosome) |
|---------------|-------------------------------------------|--------------------------|
| I (WS1)       | Dystopia canthorum, broad nasal root      | *PAX3*(2q35)             |
| II (WS2)      | no dystopia canthorum                     | *MITF*(3p14.2-p14.1),    |
|               |                                           | *SNAI2 (SLUG)* (8q11)    |
| III (WS3)     | Hypoplasia of limb muscles, contractures  | *PAX3*(2q35)             |
|               | of elbows, fingers                        |                          |
| IV (WS4)      | Hirschsprung disease                      | *EDNR3 (20q13.2-q13.3)*  |
|               |                                           | *EDNRB (13q22)*          |
|               |                                           | *SOX10 (22q13.1)*        |

Table 1: Waardenburg syndrome (WS) has been classified into four main phenotypes, which correspond to mutations of specific genes. Types I and II are the most common forms, while types III and IV are rare. All types of WS typically present with hearing loss and pigmentary abnormalities of the iris, hair, and skin. All of the abnormalities of WS involve the neural crest.
a signaling mechanism, transmitting information from the exterior is located on the surface of cells and functions as EDNRB by interacting with the endothelin receptor type B (produced from the enteric neuroblasts and influence migration of melanoblasts. EDN3, EDNRB target sites (inner ear, skin) during embryogenesis [25]. Endothelin These mutations impair the ability of melanoblasts to reach their final EDN3, EDNRB) gene. The snail 2 protein (located on chromosome 8q11) encodes the snail 2 protein, which plays a role in the development of neural crest cells during embryonic development. Neural crest cells migrate from the developing spinal cord to specific regions in the embryo and give rise to many tissues and cell types such as limb muscles, bones in the face and skull (craniofacial bones), some nerve tissue, and melanocytes. The snail 2 protein probably plays a role in the formation and survival of melanocytes. In some cases of Waardenburg syndrome, type II, both copies of the SNAI2 gene are missing. Lack of snail 2 protein may disrupt the development of melanocytes in certain areas of the skin, hair, eyes, and inner ear, leading to hearing loss and the patchy loss of pigmentation [22,23].

The SNAI2 (nail family zinc finger 2 gene) often called SLUG (located on chromosome 8q11) encodes the snail 2 protein, which plays a role in the development of neural crest cells during embryonic development. Neural crest cells migrate from the developing spinal cord to specific regions in the embryo and give rise to many tissues and cell types such as limb muscles, bones in the face and skull (craniofacial bones), some nerve tissue, and melanocytes. The snail 2 protein probably plays a role in the formation and survival of melanocytes. In some cases of Waardenburg syndrome, type II, both copies of the SNAI2 gene are missing. Lack of snail 2 protein may disrupt the development of melanocytes in certain areas of the skin, hair, eyes, and inner ear, leading to hearing loss and the patchy loss of pigmentation [22,23].

Type IV is due to either a heterozygous mutation in the SOX10 gene (encoding a transcription factor), or to homozygous mutations in the endothelin-3 (EDN3) or the endothelin B receptor (EDNRB) gene. These mutations impair the ability of melanoblasts to reach their final target sites (inner ear, eye, skin) during embryogenesis [25]. Endothelin Pathway Genes (EDN3, EDNRB) preclude premature differentiation of enteric neural crest cells and influence migration of melanoblasts. EDN3 (endothelin 3, located on chromosome band 20q13.2-q13.3) functions by interacting with the endothelin receptor type B (produced from the EDNRB gene), on the surface of cells. During early development before birth, EDN3 and EDNRB play an important role in neural crest cells. EDNRB (endothelin receptor type B, location on chromosome 13q22). The protein EDNRB is located on the surface of cells and functions as a signaling mechanism, transmitting information from the exterior to the anterior of the cell. The receptor interacts with endothelins to regulate several critical biological processes, including the development and function of blood vessels, the production of certain hormones, and the stimulation of cell growth and division.

Several mutations in the EDN3 and EDNRB genes have been identified in people with WS, type IV (also known as Waardenburg-Shah syndrome). This type of WS is characterized by changes in skin, hair, and eye coloring: hearing loss and Hirschsprung disease (HSCR), an intestinal disorder that causes severe constipation or intestinal blockage. EDN3 mutations change single nucleotides in the gene, preventing the production of a functional endothelin 3 protein. Because active endothelin 3 is necessary for the formation of enteric nerves and melanocytes, these cell types do not form normally during embryonic development. Missing enteric nerves in certain parts of the intestine cause the signs and symptoms of Hirschsprung disease [26].

SOX10 (sex determining region Y-box 10, which is mapped on chromosome 22q13.1, is important for melanin synthesis and differentiation of glial cells. During embryonic development, the SOX10 gene is active in neural crest cells. The SOX10 protein directs the activity of other genes (such as MITF) that signal neural crest cells to become more specific cell types. In particular, the SOX10 protein is essential for the formation of nerves in the large intestine (enteric nerves) and melanocytes. At least 15 mutations in the SOX10 gene have been identified in people with Waardenburg syndrome, type IV [27]. Sznaier et al. described a novel SOX10 splice site mutation (c.698-2A>C) that resulted in type IV WS without Hirschsprung disease [28]. The child presented with vivid blue eye, mental retardation, synophrys, deafness, bilateral complete semicircular canals, and peripheral neuropathy.

### Table 2: Diagnostic criteria for Waardenburg syndrome (WS) Type I. There are five major and five minor diagnostic criteria for WS (16).

| Major Criteria | Minor Criteria |
|---------------|---------------|
| 1. Sensorineural deficit hearing threshold greater than 25 dB for at least two frequencies between 250 and 4,000 Hz, without evidence of middle ear effusion and without evidence to suggest that presbyacusis or other factors account for the elevated hearing threshold. | 1. Congenital leukoderma - several areas of hypopigmented skin. |
| 2. Iris pigmented abnormality: | 2. Synophrys or medical eyebrow flare (a flaring or fanning out of the eyebrow hairs medially, toward the nasal bridge). |
| a. Two eyes of different color. | a. Evident on full-face view. |
| b. Iris bicolor/segmental heterochromia-an eye with two different colors. The pattern of the different color within the iris usually occurs in a radial segmental distribution and is clearly demarcated. | b. May or may not occur along with absence of nasofrontal depression evident on profile view (high nasal root). |
| c. Characteristic brilliant blue (sapphire) iris (alternatively described as "Waardenburg blue eye," sky-blue eyes, or hypopigmented iris). Abnormality of the stroma can be confirmed with slit lamp. | 4. Hypoplasia of alae nasi - hypoplastic lower lateral cartilages, usually resulting in narrow lower third of the nose. |
| 3. Hair hypopigmentation: | 5. Premature graying of the hair-predominance of white scalp hairs before age 30 years; white hairs appearing in the midline rather than at the temples is suggestive of WS. |
| a. White forelock: can be present at birth and then disappear later in life, with reappearance in teens or adulthood, or may appear for the first time at any age. | 2. Iris pigmentary abnormality: |
| b. Body hair: white hairs within eyebrow, eyelashes, or at other sites on the body. | a. Two eyes of different color. |
| c. Characteristic brilliant blue (sapphire) iris (alternatively described as "Waardenburg blue eye," sky-blue eyes, or hypopigmented iris). Abnormality of the stroma can be confirmed with slit lamp. | 3. Hair hypopigmentation: |
| 4. Dystopia canthorum: Lateral displacement of inner canthi, with a reduction of visible sclera medially. | a. White forelock: can be present at birth and then disappear later in life, with reappearance in teens or adulthood, or may appear for the first time at any age. |
| 5. First-degree relative previously diagnosed with WS. | b. Iris pigmented abnormality: |

**Treatment**

Waardenburg syndrome (WS) may be diagnosed at birth or early childhood. There is no specific treatment. The treatment of WS is directed toward the specific symptoms that are apparent in each individual. Early diagnosis and improvement of hearing defects...
One family has been described with two affected siblings and one sibling mixed pattern of hair pigmentation is an important diagnostic sign. Hypopigmentation, blond hair with a yellow–gray metallic sheen. The OCHS were distinct entities (Table 3) [31,33,34]. In 1967, Cross McKusick and Breen reported four siblings in an inbred Amish family, with intellectual disability, microcephaly, neurologic and ocular disorders and hypopigmentation involving skin and hair. These clinical features vary among affected individuals and possibly include hypogonadism as their female patient had undeveloped secondary sexual characteristics at age 12 years and her two younger brothers had cryptoorchidism [30-32]. A similar condition was described in 1983 by Preus, Fraser and Wiglesworth in two sisters, both presenting with skin and hair hypopigmentation, dolichocephaly, cataracts, high arched palate, deafness, and severe mental retardation (Figure 4). The oldest sister also had growth retardation, small widely spaced teeth, finger contractures, spasticity, hypochromic anemia, myopia, and moderate hydrocephalus of the lateral ventricles. These authors proposed that their patients had the same condition described by Cross but later in 1987 Patton et al. suggested that Preus and Cross OCHS were distinct entities (Table 3) [31,33,34].

CMBS is characterized by white skin (generalized hypopigmentation), blond hair with a yellow–gray metallic sheen. The mixed pattern of hair pigmentation is an important diagnostic sign. One family has been described with two affected siblings and one sibling with silver hair who was otherwise unaffected. It has been described in a Gipsy child and in South Africa. Other features reported in the setting of this syndrome include growth retardation, dolichocephaly, small eyes with cloudy corneas, cataracts, keratgyystagmus, high arched palate, small, widely spaced teeth, gingival fibromatosis, severe mental and physical retardation with spastic tetraplegia and athetosis, hypochromic anemia. Occipital cerebral atrophy, coxa valga and generalized osteoporosis have been also described. A reported case with classic findings also had urinary tract abnormality, bilateral inguinal hernia, focal interventricular septal hypertrophy of the heart, vacuolization of myeloid series cells, and distinct ultrastructural features of the skin [24,34,35].

**Clinical features**

In 1967, Cross McKusick and Breen reported four siblings in an inbred Amish family, with intellectual disability, microcephaly, neurologic and ocular disorders and hypopigmentation involving skin and hair. These clinical features vary among affected individuals and possibly include hypogonadism as their female patient had undeveloped secondary sexual characteristics at age 12 years and her two younger brothers had cryptoorchidism [30-32]. A similar condition was described in 1983 by Preus, Fraser and Wiglesworth in two sisters, both presenting with skin and hair hypopigmentation, dolichocephaly, cataracts, high arched palate, deafness, and severe mental retardation (Figure 4). The oldest sister also had growth retardation, small widely spaced teeth, finger contractures, spasticity, hypochromic anemia, myopia, and moderate hydrocephalus of the lateral ventricles. These authors proposed that their patients had the same condition described by Cross but later in 1987 Patton et al. suggested that Preus and Cross OCHS were distinct entities (Table 3) [31,33,34].

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**Genetics/pathogenesis**

An interstitial deletion [del(3)(q27.1-1q29)] has been identified in the paternal chromosome of a 4-year-old female but the molecular defect of this extremely rare disorder is still unknown [30,35].

In the case-report of Patton et al. the electron microscopy confirmed that epidermal melanocyte numbers were normal. The cells also appeared structurally normal and possessed dendrites. There was no evidence of a structural abnormality of the melanosomal matrix. Most melanosomes were in stage II or III with fewer in stage IV. Keratinocytes adjacent to melanocytes were often oedematous and suprabasal cells were vacuolated. The keratinocyte oedema was associated with intercellular granular material, which together might have impeded melanosomal transfer. No autophagic (lysosomal) inclusions or giant melanosomes were observed within melanocytes, keratinocytes, or macrophages [34]. Blood tyrosine levels are normal and the light-colored hair pigments poorly in tyrosine solution [36]. The generalized hypopigmentation and the mental retardation appear to be linked. Neurones and melanocytes are embryologically derived from the same origin in the neuroectoderm. It appears that melanocytes, or possibly the melanin pigments they produce, are responsible for controlling the functional development of certain neural pathways [34].

**Conclusion**

We herein describe the clinical and genetic characteristics of three selected genodermatoses, namely Piebaldism, Waardenburg syndrome and Cross-McKusick– Breen syndrome. The common feature of these disorders is the mutation-based de-arrangements of the normal process
by which precursors of melanocytes develop at the neural crest and migrate to different peripheral sites. Although rare and phenotypically diverse, the study of these diseases has yielded significant knowledge on the genes that regulate the migration of melanocytes and the mechanisms that control skin, hair and eye pigmentation.

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