Abstract: Syndromic hereditary hearing impairment (HHI) is a clinically and etiologically diverse condition that has a profound influence on affected individuals and their families. As cutaneous findings are more apparent than hearing-related symptoms to clinicians and, more importantly, to caregivers of affected infants and young individuals, establishing a correlation map of skin manifestations and their underlying genetic causes is key to early identification and diagnosis of syndromic HHI. In this article, we performed a comprehensive PubMed database search on syndromic HHI with cutaneous abnormalities, and reviewed a total of 260 relevant publications. Our in-depth analyses revealed that the cutaneous manifestations associated with HHI could be classified into three categories: pigment, hyperkeratosis/nail, and connective tissue disorders, with each category involving distinct molecular pathogenesis mechanisms. This outline could help clinicians and researchers build a clear atlas regarding the phenotypic features and pathogenetic mechanisms of syndromic HHI with cutaneous abnormalities, and facilitate clinical and molecular diagnoses of these conditions.

Keywords: syndromic hereditary hearing impairment; cutaneous abnormalities; genetic diagnosis; precision medicine

1. Introduction

Sensorineural hearing impairment (SNHI) is the most common form of inherited sensory defect, which occurs in approximately 1.9/1000 live births [1]. More than 50% of SNHI cases in children can be attributed to genetic causes, and are classified as hereditary hearing impairment (HHI) [2]. Over the past two decades, the genetic causes of HHI have been decoded rapidly, especially with the advent of next-generation sequencing (http://hereditaryhearingloss.org) [3]. Among the deafness genes known, some are associated with syndromic HHI, with symptoms in organ systems outside the auditory pathway. Patients suffering from various forms of syndromic HHI additionally present with skin abnormalities. The goals of this review were to perform a literature survey on comprehensive animal and human studies and to outline the molecular mechanisms underlying HHI with cutaneous abnormalities.
2. Materials and Methods

Our search strategy was based on using Online Mendelian Inheritance in Man (OMIM) and PubMed databases for retrieval of suitable articles relevant to our topic of interest. A collection of these publications was stored and managed on EndNote X9 (Thomson Reuters, New York City, NY, USA). Publications were eligible only if they were relevant to HHI associated with cutaneous abnormalities. Affected patients included in case reports or series were considered to be of interest only if relevant phenotypes, including abnormal cutaneous, hair, or nail findings, as well as SNHI were observed. Publications focusing on individuals with HHI and developmental disorders (e.g., distinctive facial characteristics, congenital heart defect, developmental delay, kyphosis, among others), who did not present with abnormal skin, hair, or nail findings, were not included for discussion in the present review. Studies in which the subjects discussed presented with abnormal cutaneous findings due to other proven diseases (e.g., acanthosis nigricans due to diabetes mellitus) were also excluded. A flowchart of the search strategy is shown in Figure 1.

![Flowchart of the search strategy](image)

Figure 1. Article selection.

3. Various Types of HHI Present with Cutaneous Abnormalities

3.1. Search Results

Forty-eight entries in the OMIM database with distinct “MIM (Mendelian Inheritance in Man) numbers” were selected, and a total of 260 publications were retrieved from the PubMed database, including original articles \(n = 154\), case reports \(n = 74\), and literature reviews \(n = 32\), to perform the analysis. The quality of the articles included was meticulously evaluated based on the degree of relevance to the topic of this review. A detailed list sorted by phenotypes (Table 1) is included in the following paragraph. The pathogenesis of these syndromes is covered separately by the fourth section of this article.
Table 1. Summary of syndromic hereditary hearing impairment (HHI) with cutaneous abnormalities.

| Syndrome                              | Genes Involved | OMIM Number         | Mode of Inheritance | Clinical Findings Other Than SNHI                                                                 | Ref.       |
|---------------------------------------|----------------|---------------------|---------------------|--------------------------------------------------------------------------------------------------|-----------|
| **Pigment disorders**                 |                |                     |                     |                                                                                                  |           |
| Waardenburg syndrome type 1           | PAX3           | 193500              | AD                  | Pigmentary abnormalities of the hair, skin, and eyes, dystopia canthorum                            | [4–6]     |
| Waardenburg syndrome type 2           | MITF, SNAI2,  | 184745, 193510,    | AD, AR              | Pigmentary abnormalities of the hair, skin, and eyes                                               | [4,5,7–9] |
|                                       | SOX10, KITLG   | 600193, 606662,     |                     |                                                                                                  |           |
|                                       |                | 608890, 611584      |                     |                                                                                                  |           |
| Waardenburg syndrome type 3           | PAX3           | 148820              | AD, AR              | Pigmentary abnormalities of the hair, skin, and eyes, dystopia canthorum, upper limb abnormalities   | [4,5]     |
| Waardenburg syndrome type 4           | EDNRB, EDN3,  | 277580, 613265,     | AD, AR              | Pigmentary abnormalities of the hair, skin, and eyes, Hirschsprung disease                         | [4,5]     |
|                                       | SOX10          | 613266              |                     |                                                                                                  |           |
| Tietz albinism-deafness syndrome      | MITF           | 103500              | AD                  | Albinism, lack of retinal pigmentation, absent eyebrows                                            | [10]      |
| COMMAD syndrome                      | MITF           | 617306              | AR                  | Microphthalmia, coloboma, cranial dysmorphism, cataract, osteopetrosis, pigmentary abnormalities of the hair, skin, and eyes | [11]      |
| Histiocytosis-lymphadenopathy plus syndrome | SLC29A3       | 602782              | AR                  | Hyperpigmentation, hypertrichosis, lymphadenopathy, hepatosplenomegaly, heart anomalies, and hypogonadism | [12]      |
| Noonan syndrome with multiple lentigines | PTPN11, RAFL1, BRAF | 151100, 611554, 613707 | AD                  | Multiple lentigines, ocular hypertelorism, growth retardation, electrocardiographic conduction abnormalities, pulmonary stenosis, abnormal genitalia | [13–16] |
| Vitiligo-associated multiple autoimmune disease susceptibility | NLRP1 | 606579              | unknown             | Patchy depigmentation of the skin and hair, elevated risk of autoimmune diseases                  | [17]      |
| Xeroderma pigmentosum                | XPA, XPC, DDB2 (XPE), ERCC2 (XPD), ERCC3 (XPB), ERCC4 (XP), ERCC5 (XPG), ERCC6 (CSB), POLH (XPV) | 610651, 278760, 278780, 278750 | AR                  | Cutaneous photosensitivity, microphthalmia, cataracts, optic atrophy, pigmentary retinal degeneration, neurological impairments, growth defects | [18–21] |
| Cockayne syndrome                    | ERCC6, ERCC8 (CSA) | 133540, 216400         | AR                  | Cutaneous photosensitivity, thin and dry hair, pigmentary retinopathy, dental caries, progeroid appearance, characteristic stance in ambulatory patients | [22–25] |
| Syndrome                                      | Genes Involved | OMIM Number | Mode of Inheritance | Clinical Findings Other Than SNHI                                                                 | Ref.          |
|-----------------------------------------------|----------------|-------------|---------------------|--------------------------------------------------------------------------------------------------|--------------|
| **Hyperkeratoses**                            |                |             |                     |                                                                                                  |              |
| Palmoplantar keratoderma with deafness        | GJB2           | 148350      | AD                  | Hyperkeratosis of the palms and soles                                                              | [26,27]      |
| Vohwinkel syndrome                            | GJB2           | 124500      | AD                  | Palmoplantar hyperkeratosis, epidermal thickening of the knuckles and knees, pseudoainhum or autoamputation of the fingers and toes | [28–30]     |
| Bart-Pumphrey syndrome                        | GJB2           | 149200      | AD                  | Palmpoplantar hyperkeratosis, knuckle pads, leukonychia                                           | [31–33]      |
| Hystrix-like ichthyosis with deafness         | GJB2           | 602540      | AD                  | Erythroderma, hyperkeratosis, hypotrichosis of eyebrows, eyelids, and scalp                       | [34,35]      |
| Keratitis-ichthyosis-deafness syndrome        | GJB2, GJB6     | 148210      | AD                  | Keratopachydermia and constrictions of the fingers and toes, loss of eyebrows and eyelashes       | [34,36]      |
| **Nail disorders**                            |                |             |                     |                                                                                                  |              |
| Autosomal-dominant deafness-onychodystrophy syndrome | ATP6V1B2     | 124480      | AD                  | Dystrophic or hypoplastic nails, syndactyly, triphalangeal thumbs, tooth agenesis                  | [37–40]      |
| Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures syndrome | TBC1D24       | 220500      | AR                  | Dystrophic or hypoplastic nails, syndactyly, triphalangeal thumbs, tooth agenesis, mental retardation, seizures | [41–44]      |
| Heimler syndrome 1                            | PEX1           | 234580      | AR                  | Beau lines, enamel hypoplasia in the permanent dentition                                           | [45–54]      |
| Heimler syndrome 2                            | PEX6           | 616617      | AR                  | Beau lines, enamel hypoplasia in the permanent dentition                                           | [45,47–53]   |
| Nail-patella syndrome                         | LMX1B          | 161200      | AD                  | Dysplastic or hypoplastic nails, absent or hypoplastic patellae, iliac horns, abnormality of the elbows interfering with pronation and supination, nephropathy | [56–61]      |
| Nephropathy with pretibial epidermolysis bullosa and deafness | CD151         | 609057      | unknown             | Multiple, recurrent, infected skin blisters of the legs, followed by atrophy, nail dystrophy, bilateral lacrimal duct stenosis, proteinuria in the nephrotic range | [62–65]      |
Table 1. Cont.

| Syndrome                                      | Genes Involved | OMIM Number | Mode of Inheritance | Clinical Findings Other Than SNHI                                                                 | Ref.        |
|-----------------------------------------------|----------------|-------------|---------------------|-------------------------------------------------------------------------------------------------|-------------|
| Connective tissue disorders                   |                |             |                     |                                                                                                |             |
| Brittle cornea syndrome 1                     | ZNF469         | 229200      | AR                  | Hyperelasticity of the skin, hypermobility of the joints, blue sclerae, keratoconus, keratoglobus | [66–68]     |
| Brittle cornea syndrome 2                     | PRDM5          | 614170      | AR                  | Hyperelasticity of the skin, hypermobility of the joints, blue sclerae, keratoconus, keratoglobus | [66,67,69, 70] |
| Ehlers-Danlos syndrome musculocontractural type 1 | CHST14         | 601776      | AR                  | Hypermobility of the joints, cranial dysmorphism, contracture of the thumbs and fingers, adducted thumb, clubfoot, kyphoscoliosis | [71–75]     |
| Congenital symmetric circumferential skin creases type 1 | TUBB           | 156610      | AD                  | Excess skin, ringed creases of the limbs, hypertrichosis, mental retardation, facial dysmorphism, neurological abnormalities | [76,77]     |
| Congenital symmetric circumferential skin creases type 2 | MAPRE2         | 616734      | AD                  | Excess skin, ringed creases of the limbs, hypertrichosis, mental retardation, facial dysmorphism, neurological abnormalities | [77–79]     |
| Microphthalmia with linear skin defects syndrome | HCCS           | 309801      | XLD                 | Irregular linear areas of erythematous skin hypoplasia, microphthalmia, short stature, corneal opacities, developmental delay, agenesis of the corpus callosum | [80–83]     |
| Familial cold autoinflammatory syndrome 1      | NLRP3          | 120100      | AD                  | Episodic urticarial rash and swelling of the extremities after exposure to cold                    | [84,85]     |
| Familial cold autoinflammatory syndrome 2      | NLRP12         | 611762      | AD                  | Episodic urticarial rash, fever, headache, lymphadenopathy, arthralgia, and myalgia after exposure to cold | [86–88]     |
| Muckle-Wells syndrome                          | NLRP3          | 191900      | AD                  | Episodic rash, fever, arthralgia, and renal amyloidosis                                           | [89–91]     |
| Chronic infantile neurologic cutaneous and articular syndrome | NLRP3         | 607115      | AD                  | Persistent and migratory urticarial rash, progressive visual defect and neurologic impairment, and joint abnormalities | [92–95]     |
| Others                                        |                |             |                     |                                                                                                |             |
| Cornelia de Lange syndrome                    | NIPBL, SMC1A, SMC3, RAD21, HDAC8 | 122470, 300590, 610759, 614701, 300882 | AD, XLD | Hemangioma, facial dysmorphisms, including hypertrichosis, synophrys, and bushy eyebrows | [96]        |

SNHI: sensorineural hearing loss. AD: autosomal dominant. AR: autosomal recessive. XLD: X-linked dominant.
3.2. HHI with Pigment Disorders

3.2.1. Waardenburg Syndrome (WS)

With an estimated prevalence of 1/42,000, WS is a rare, heterogeneous condition, the features of which include white forelock, depigmented patches of the skin, and SNHI [4,5,97]. These features are characteristic of type 2 WS, while additional clinical symptoms define other types of WS [98]. Patients with type 1 WS present with dystopia canthorum; patients with type 3 WS, a more severe form than type 1 WS, present with dystopia canthorum and musculoskeletal abnormalities of the arms and hands [99,100]. In contrast, patients with type 4 WS present with Hirschsprung disease [101].

WS types 2 and 4 can be further classified into subtypes according to the genetic origins. A summary of the subtypes of WS and the genes affected are shown in Table 2. Among the different subtypes of WS, types 2B and 2C are linked to pathogenic variants in unidentified genes mapping to 1p21–p13.3 and 8p23, respectively [98,101–106].

| Subtypes of WS Affected Genes Locations |
|----------------------------------------|-----------------|
| Type 1 | P AX3 | 2q36.1 |
| Type 2A | MITF | 3p13 |
| Type 2A with ocular albinism | MITF, TYR | 3p13, 11q14.3 |
| Type 2B | - | 1p21–p13.3 |
| Type 2C | - | 8p23 |
| Type 2D | SNAI2 | 8q11.21 |
| Type 2E | SOX10 | 22q13.1 |
| Type 2, subtype not designated | KITLG | 12q21.32 |
| Type 3 | P AX3 | 2q36.1 |
| Type 4A | EDNRB | 13q22.3 |
| Type 4B | EDN3 | 20q13.32 |
| Type 4C | SOX10 | 22q13.1 |

WS types 2A and 2 with ocular albinism (WS2-OA) both result from pathogenic variants in the microphthalmia-associated transcription factor gene (MITF), and present with SNHI and pigment disorders. WS2-OA also results from pathogenic variants in the TYR gene, the main function of the protein product of which is converting tyrosine into melanin [107,108]. Upstream to MITF, pathogenic variants in KITLG have been found to cause WS type 2 [8,9].

Other pathogenic variants resulting in HHI with pigment disorders include those in PAX3, SOX10, EDNRB, EDN3, and SNAI2 genes. Pathogenic variants in PAX3 lead to WS types 1 and 3, and those in SOX10 to WS types 2E and 4C [109]. Patients with a defective EDNRB signaling pathway develop either WS types 4Aand 4B, or ABCD syndrome (albinism, black lock of hair, cell migration disorder of gut neurocytes, and sensorineural deafness) [110,111]. Manifestations of these syndromes include Hirschsprung disease, depigmented patches of the skin, white eyelashes, pale blue iridis, and white forelock [103,112]. Homozygous deletions of SNAI2 have been detected in patients with WS type 2D [106].

3.2.2. Tietz Albinism-Deafness Syndrome (TADS)

TADS is a rare autosomal-dominant disease featuring SNHI, generalized pigment loss, and lack of retinal pigmentation [113]. Premature graying of hair during adolescence was observed in a patient [10,107]. Pathogenic variants in MITF, including 3-bp del (p.Arg217del), and missense variant c.630C>G (p.Asn210Lys) identified respectively in two
families, result in TADS [107, 114, 115]. Hypopigmentation stems from disrupted transfer of melanosomes from melanocytes to keratinocytes [10]. Although TADS results from alterations in a gene linked to WS type 2, patients do not present with heterochromia or pigmented patches [4, 10, 114].

### 3.2.3. COMMAD Syndrome

COMMAD syndrome encompasses coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness. Compound heterozygous *MITF* mutations have been detected in two unrelated families with COMMAD syndrome [11]. In contrast to WS type 2A and TADS, which are associated with autosomal-dominant *MITF* mutations, COMMAD syndrome seems to be associated with an autosomal recessive inheritance of *MITF*, suggesting a crucial role for *MITF* in ocular morphogenesis and bone homeostasis [11].

### 3.2.4. Histiocytosis-Lymphadenopathy Plus Syndrome

The “histiocytosis-lymphadenopathy plus syndrome” family is a generic term for the H syndrome, Faisalabad histiocytosis (FHC), sinus histiocytosis with massive lymphadenopathy (SHML), and pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome (PHID) [12]. In the literature, clinical reports and molecular studies are sparse, since it was only recently discovered. The patients had severe SNHI and extensive hyperpigmentation with dark, long hairs. Histologically, polyclonal perivascular lymphohistiocytic infiltrations of the dermis and subcutis were found in hypertrichotic lesions [12, 116]. This group of diseases is caused by pathogenic variants in *SLC29A3*, which encodes ENT3, equilibrative nucleoside transporter 3 [12, 116–118]. This enzyme is in intracellular membranes and mediates cross-membrane nucleoside transportation [119]. Defective ENT3 impairs mitochondrial and lysosomal functions, as well as macrophage homeostasis [12].

### 3.2.5. Noonan Syndrome with Multiple Lentigines (NSML)

NSML is a rare autosomal-dominant disease without a credible record of global or regional prevalence to date [15]. As its former name “LEOPARD syndrome” indicates, the syndrome features a myriad of clinical manifestations, including multiple lentigines, conduction abnormalities on electrocardiogram, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and SNHI [13, 15, 16]. Pathogenic variants in *PTPN11, RAF1*, and *BRAF* genes, encoding parts of the RAS-MAPK (Mitogen-activated protein kinase) signaling cascade, result in NSML types 1, 2, and 3, respectively [14, 120, 121]. The larger entity, Noonan syndrome (NS), is an autosomal-dominant disease featuring short stature, facial dysmorphia, congenital heart disease, pulmonary valve stenosis, and SNHI, but without multiple lentigines [122]. NS is caused by RAS-MAPK pathway-debilitating variants in *PTPN11, RAF1, BRAF, SOS1, KRAS*, among others [122, 123].

### 3.2.6. Vitiligo-Associated Multiple Autoimmune Disease Susceptibility 1 (VAMAS1)

VAMAS1 features patchy depigmentation of the hair and skin due to the loss of melanocytes, SNHI in certain cases, and a propensity of developing autoimmune thyroid disease, rheumatoid arthritis, and systemic lupus erythematosus [17, 124]. The pathogenic variant p.L155H of *NLRP1* has been identified to cause VAMAS1 [125]. *NLRP1* encodes the sensor component of the NLRP1 inflammasome. In response to pathogens, drugs, or damage-associated signals, this protein is recruited, possibly along with PYCARD (PYD And CARD Domain Containing) protein, to assemble the NLRP1 inflammasome and facilitates innate immunity and inflammation [17, 126]. Autoimmune response has also been identified in Vogt–Koyanagi–Harada disease (VKHD), another rare multisystem inflammatory disease characterized by pan-uveitis, SNHI, vitiligo, and neurological deficits. However, current studies suggest a melanocyte-specific Th1 cytokine response in VKHD [127, 128].
3.2.7. Genophotodermatoses

Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) are autosomal recessive genophotodermatoses resulting from variants in genes involved in DNA repair [22,129,130]. The prevalence of XP is 1/1,000,000 in Europe and the United States (US), and higher in Japan, the Middle East, and North Africa, whereas CS holds a prevalence of 2–3/1,000,000 in the US and Europe [131,132].

Photosensitivity, SNHI, and neurologic dysfunction are shared cardinal features of XP and CS [21,22,129,133,134]. Lentiginous macules and poikiloderma are more severe in XP, while loss of subcutaneous orbital fat is distinctive of CS [24,135]. Manifestations of these genophotodermatoses can be attributed to accumulated unrepaired DNA damage following defects in key components of the DNA nucleotide excision repair (NER) pathway. Pathogenic variants in ERCC6 and ERCC8 lead to CS types B and A, respectively. Pathogenic variants in XPA, XPC, RAD2, DDB1, ERCC2, ERCC3, ERCC4, ERCC5, and ERCC6 lead to XP groups A-G. Pathogenic variants in POLH result in a variant type of XP, which is called XPV [19,20,130,131,134,136].

3.3. HHI with Hyperkeratosis

Gap junction-related hyperkeratosis syndromes include palmoplantar keratoderma (PPK) with deafness, Vohwinkel syndrome, Bart-Pumphrey syndrome, hystrix-like ichthyosis with deafness (HID), and keratitis-ichthyosis-deafness syndrome (KID). This is a subgroup of the more generic condition PPKs, but epidemiological studies are lacking due to its rarity [34,137–139].

SNHI is a shared manifestation among PPK with deafness, Bart-Pumphrey syndrome, HID, KID, and the classic form of Vohwinkel syndrome. By contrast, patients with the variant form of Vohwinkel syndrome do not suffer from SNHI. As for cutaneous manifestation, generalized spiky hyperkeratotic skin is characteristic of HID and KID, while hyperkeratosis is mostly limited to the fingers, palms, and soles in PPK with deafness, Vohwinkel syndrome, and Bart-Pumphrey syndrome [139]. Leukonychia and thickening of the nails have also been reported in cases with Bart-Pumphrey syndrome [31,32,140–142].

The five conditions listed in this subgroup share a common genetic cause, i.e., pathogenic variants in GJB2 [31,143–148]. In addition, pathogenic variants in the GJB6 gene that encodes connexin 30 (Cx30) have also been identified in a family clinically diagnosed with KID [149].

GJB2 and GJB6 variants cause both syndromic and non-syndromic HHI. The causal relationship of non-syndromic HHI and pathogenic variants in GJB2 and GJB6 have been well-established. Pathogenic variants in GJB2 serve as the most common cause of autosomal recessive HHI and 20% of non-syndromic hearing loss overall [150,151]. GJB6 variants are less prevalent than GJB2 variants but have been identified in 8% of patients with known GJB2 variants [152]. Whether variants in specific domains of GJB2 or GJB6 genes cause syndromic or non-syndromic HHI remains to be elucidated.

3.4. Nail Disorders

3.4.1. Autosomal-Dominant Deafness-Onychodystrophy (DDOD) Syndrome

With a prevalence of less than 1/1,000,000, DDOD features severe SNHI, hypoplastic or dystrophic nails, and occasionally, hypoplastic teeth [37,38]. DDOD is associated with pathogenic variants in the ATP6V1B2 gene [39,40].

3.4.2. Deafness, Onychodystrophy, Osteodystrophy, Mental Retardation, and Seizures (DOORS) Syndrome

With an estimated prevalence of less than 1/1,000,000, the autosomal recessively inherited DOORS differs from DDOD regarding neurological symptoms, including mental retardation and seizures [41,153–155]. Pathogenic variants in TBC1D24 are the causative genetic alterations associated with DOORS [42,43,156–159].
3.4.3. Heimler Syndrome and Other Peroxisomal Biogenesis Disorders (PBDs)

PBDs are a spectrum of autosomal recessive disorders of different severity, of which Zellweger syndrome (ZS) is the most severe form; neonatal adrenoleukodystrophy (NALD) presents with milder symptoms, and infantile Refsum disease (IRD) and Heimler syndrome constitute the mildest forms. The prevalence of PBDs is 1/50,000 and 1/500,000 in North America and Japan, respectively, while epidemiological figures on Heimler syndrome are to be determined [51,160,161]. PBDs result from pathogenic variants in peroxin-encoding genes, i.e., PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX11β, PEX12, PEX13, PEX14, PEX16, PEX19, and PEX26 [50]. Heimler syndromes 1 and 2 are at the mildest end of the PBD spectrum, and are caused by pathogenic variants in PEX1 and PEX6, respectively [47,51,54]. Errors in the production of peroxins result in impaired myelin sheath formation and neurological deficits, including neonatal seizures, hypotonia, and developmental delays. Decreased peroxisome functionality in the liver and kidneys gives rise to the associated symptoms, including hepatomegaly, intrahepatic biliary dysgenesis, and hydronephrosis. SNHI and distinctive craniofacial features are also cardinal features of PBDs. Nail abnormalities, including Beau lines and leukonychia, have been reported in patients with Heimler syndrome [46,51,53–55].

3.4.4. Nail-Patella Syndrome (NPS)

NPS is an autosomal dominantly inherited syndrome with a prevalence of 1/50,000 live births. Nail dysplasia is the cardinal dermatologic manifestation of NPS. Nail changes include partially exposed and/or narrow nail beds, median or partial median clefts, dystrophic nail surfaces, and absence of nails. Fifth finger clinodactyly, hypextensibility of the proximal interphalangeal joint, loss of creases over the distal interphalangeal joint and triangular lunulae have been reported in NPS patients. Other key features include malformation of dorsal mesenchyme-derivatives, including muscles, tendons, and the patella, along with ocular or renal involvement [162–165]. Hearing loss has also been reported in patients with NPS [59]. Genetically, pathogenic variants in LMX1B are considered to be causative of NPS [57,59,166,167].

3.4.5. Nephropathy with Pretibial Epidermolysis Bullosa and Deafness (NPEBD)

The only three cases with NPEBD feature nail dystrophy, blisters in the lower extremities, SNHI, and proteinuria in the nephrotic range [65]. Single-nucleotide insertion (383_384insG) in CD151, a gene encoding a component of hemidesmosomes, has been found in all cases. This result implies a role for CD151 in the maintenance of the normal structure and function of the skin, inner ear, and the glomeruli and tubules in the kidney [62–64].

3.5. HHI with Connective Tissue Disorders

3.5.1. Hyperelasticity of the Skin, Excess Skin, or Hypermobility of the Joints

Brittle cornea syndrome (BCS), Ehlers-Danlos syndrome musculocontractural type 1 (EDSMC1), congenital symmetric circumferential skin creases (CSCSC) types 1 and 2, and microphthalmia with linear skin defects syndrome (MLS) are connective tissue disorders that present with distinct cutaneous findings and hearing impairment. Epidemiological data are scant due to the rarity of these conditions.

BCS1 and BCS2 are characterized by hyperelasticity of the skin, hypermobility of the joints, blue sclerae, keratoconus, and keratoglobus. Mixed conductive and sensorineural hearing impairments have been reported in cases of BCS, with frequent manifestations that are milder and of later onset than the ophthalmic symptoms. BCS1 and BCS2 result from pathogenic variants in ZNF469 and PRDM5, respectively [66,69,168–171].

EDSMC1 is characterized by dysmorphisms throughout the musculoskeletal system, easy bruising, joint hypermobility, and hearing impairment, in certain cases. EDSMC1 can be attributed to pathogenic variants in CHST14 [67,72,74,172,173].
Patients with CSCSC1 and CSCSC2 feature excess skin and ringed creases, as well as hearing impairment [77,174]. CSCSC is considered a tubulopathy. Accordingly, pathogenic variants in TUBB and MAPRE2 are the causative genetic alterations associated with CSCSC1 and CSCSC2, respectively [77,79,174].

Microphthalmia with linear skin defects syndrome (MLS), or linear skin defects with multiple congenital anomalies 1 (LSDMCA1), also features linear skin defects and hearing impairment, and is caused by pathogenic variants in the holocytochrome c-type synthase-encoding HCCS gene [175–179].

3.5.2. Cryopyrin-Related Autoinflammatory Syndromes (CAPS)

A spectrum of autosomal-dominant autoinflammatory syndromes of different severities, including Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndromes 1 and 2 (FCAS1, FCAS2), and chronic infantile neurologic cutaneous and articular (CINCA) syndrome, are related to cryopyrin. The prevalence of CAPS in France and the USA is estimated to be 1/360,000 and 1–2/1,000,000 individuals, respectively [180,181]. Patients present with urticaria, rash, or limb swelling, aggravated by cold temperature [182,183]. SNHI may result from inflammatory processes in the cochlea [180,184–186]. FCAS2 arises from pathogenic variants in NLRP12, while MWS, FCAS1, and CINCA syndrome can be attributed to gain-of-function pathogenic variants in the NLRP3 gene [90,185].

3.6. Others

Cornelia de Lange syndrome, with an overall prevalence of 1.6–2.2/100,000, is a mostly sporadic condition characterized by multiple organ-system defects [187]. Patients present with dysmorphic face and upper extremities, and growth and mental retardation. Hearing impairment, either sensorineural or conductive, is nearly ubiquitous [96,188–190]. The skin is mostly spared, but cavernous hemangiomas have been observed in a case with Cornelia de Lange syndrome 1 [190–194]. NIPBL, SMC1A, SMC3, RAD21, and HDAC8 are the five genes associated with Cornelia de Lange syndrome [191–195].

3.7. Frequency of SNHI in HHI with Cutaneous Abnormalities

The frequency of SNHI differs among various syndromic HHI with cutaneous abnormalities. For instance, SNHI has been found in over 70% of cases with WS, TADS, COMMA1D, or NSML syndromes [11,15,97,114]; and in approximately half of patients with other syndromes such as histiocytosis-lymphadenopathy plus syndrome [196]. On the contrary, the frequency of SNHI is difficult to estimate in rarer conditions such as NPS, DOORS, or DDOD.

4. Molecular Mechanisms Underlying Various Types of HHI with Cutaneous Abnormalities

The pathogenesis behind some of the syndromes discussed in the present study has been documented in the literature. Generally, cutaneous manifestations associated with HHI can be classified into three categories: pigment, hyperkeratosis/nail, and connective tissue disorders (Table 3). We herein summarize the molecular mechanisms underlying syndromic HHI with different cutaneous involvements.
Table 3. Molecular mechanisms underlying syndromic hereditary hearing impairment (HHI) with cutaneous abnormalities and expression of the affected genes in the inner ear and epidermis.

| Affected Molecular Pathways | Phenotype                          | Gene Symbol | Fold Change (Hair Cell/Non-Hair Cell) in the Inner ear | Main Expressors in the Epidermis |
|-----------------------------|------------------------------------|-------------|--------------------------------------------------------|---------------------------------|
| **HHI with pigment disorders** |                                    |             |                                                        |                                 |
| MITF-related                | Waardenburg syndrome               | MITF        | 0.17                                                   | K, M                            |
| PAX3                        |                                    |             | 0.15                                                   | K, L, M                         |
| SOX10                       |                                    |             | 0.21                                                   |                                  |
| Non-MITF-related            | Waardenburg syndrome               | EDNRB       | 0.08                                                   | low expression in K, M          |
| EDN3                        |                                    |             | 0.09                                                   | no data                         |
| SNAI2                       |                                    |             | 0.14                                                   | F, K, L, M                      |
| RAS-MAPK signaling          | Noonan syndrome with multiple lentigines | PTPN11    | 1.27                                                   | diffuse in epidermal cells |
| RAF1                        |                                    |             | 1.35                                                   | low expression                  |
| BRAF                        |                                    |             | 2.77                                                   | K, L, M                         |
| XPA                         |                                    |             | 3.00                                                   | K, L, M                         |
| XPC                         |                                    |             | 1.06                                                   | K, M                            |
| DDB2 (XPE)                  |                                    |             | 1.34                                                   | K, L, M                         |
| ERCC2 (XPD)                 |                                    |             | 1.05                                                   | K, L, M                         |
| ERCC3 (XBP)                 |                                    |             | 0.84                                                   | K, L, M                         |
| ERCC4 (XPF)                 |                                    |             | 1.57                                                   | K                                |
| ERCC5 (XPG)                 |                                    |             | 1.03                                                   | K, L                            |
| ERCC6 (CSB)                 |                                    |             | 6.04                                                   | no data                         |
| POLH (XPV)                  |                                    |             | 1.09                                                   | K, L, M                         |
| DNA repair                  | Xeroderma pigmentosus              |             |                                                        |                                 |
| XPA                         |                                    |             | 3.00                                                   | K, L, M                         |
| XPC                         |                                    |             | 1.06                                                   | K, M                            |
| DDB2 (XPE)                  |                                    |             | 1.34                                                   | K, L, M                         |
| ERCC2 (XPD)                 |                                    |             | 1.05                                                   | K, L, M                         |
| ERCC3 (XBP)                 |                                    |             | 0.84                                                   | K, L, M                         |
| ERCC4 (XPF)                 |                                    |             | 1.57                                                   | K                                |
| ERCC5 (XPG)                 |                                    |             | 1.03                                                   | K, L                            |
| ERCC6 (CSB)                 |                                    |             | 6.04                                                   | no data                         |
| POLH (XPV)                  |                                    |             | 1.09                                                   | K, L, M                         |
| Cockayne syndrome           |                                    |             |                                                        |                                 |
| XPA                         |                                    |             | 3.00                                                   | K, L, M                         |
| XPC                         |                                    |             | 1.06                                                   | K, M                            |
| DDB2 (XPE)                  |                                    |             | 1.34                                                   | K, L, M                         |
| ERCC2 (XPD)                 |                                    |             | 1.05                                                   | K, L, M                         |
| ERCC3 (XBP)                 |                                    |             | 0.84                                                   | K, L, M                         |
| ERCC4 (XPF)                 |                                    |             | 1.57                                                   | K                                |
| ERCC5 (XPG)                 |                                    |             | 1.03                                                   | K, L                            |
| ERCC6 (CSB)                 |                                    |             | 6.04                                                   | no data                         |
| POLH (XPV)                  |                                    |             | 1.09                                                   | K, L, M                         |
| **HHI with hyperkeratosis or nail disorders** |                               |             |                                                        |                                 |
| Palmoplantar keratoderma with deafness, Vohwinkel syndrome, Bart-Pumphrey syndrome, hystrix-like ichthyosis-deafness syndrome, keratitis-ichthyosis-deafness syndrome | GJB2 | 0.31                                                   | K, L, M                         |
| Keratitis-ichthyosis-deafness syndrome | GJB6 | 0.10                                                   | no data |

Inflammasome assembly

Vitiligo-associated multiple autoimmune disease susceptibility

| NLRP1 | nlrp1a: 0.43 | nlrp1b: 4.03 | K, L |
Table 3. Cont.

| Affected Molecular Pathways | Phenotype                                             | Gene Symbol | Fold Change (Hair Cell/Non-Hair Cell) in the Inner ear | Main Expressors in the Epidermis |
|-----------------------------|-------------------------------------------------------|-------------|--------------------------------------------------------|----------------------------------|
| Vacuolar proton transportation | Dominant deafness-onychodystrophy                      | ATP6V1B2    | 2.97                                                   | K, L, M                          |
| Transportation of vesicles  | Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures | TBC1D24    | 0.75                                                   | not detected                     |
| Peroxisome biogenesis       | Heimler syndrome 1                                     | PEX1        | 1.62                                                   | not detected                     |
|                             | Heimler syndrome 2                                     | PEX6        | 0.86                                                   | low expression                   |
| LIM homeobox-dependent transcription | Nail-patella syndrome                                | LMX1B       | 3.04                                                   | no data                          |
| Formation and maintenance of hemidesmosomes | Nephropathy with pretibial epidermolysis bullosa and deafness | CD151     | 0.65                                                   | K, M                             |

| HHI with connective tissue disease |
|------------------------------------|
| Extracellular matrix regulation     | Brittle cornea syndrome                             | ZNF469      | No data                                               | K, L, M                          |
|                                    | Ehlers-Danlos syndrome, musculocontractural type 1  | PRDM5       | 0.55                                                  | no data                          |
|                                    |                                                     | CHST14      | 0.22                                                  | F, M                             |

| Microtubule dimerization and dynamics | Congenital symmetric circumferential skin creases 1 | TUBB | tubb1: 1.49, tubb2a: 1.24, tubb2b: 3.46, tubb3: 22.03, tubb4a: 0.57, tubb4b: 3.30, tubb5: 0.62, tubb6: 0.43 | F, M |
|                                    | Congenital symmetric circumferential skin creases 2 | MAPRE2      | 0.85                                                  | low expression in F, K, M        |

| Oxidative phosphorylation and apoptosis | Microphthalmia with linear skin defects syndrome | HCCS | 0.63                                                  | low expression in F, L, K, M     |
| Inflammasome assembly                | Cryopyrin-associated periodic syndrome             | NLRP3      | 0.05                                                  | K, M                             |
|                                    |                                                     | NLRP12     | No data                                               | L, M                             |

1 Fold change (hair cell/non-hair cell) denotes the ratio of hair cells to non-hair cells in mouse utricle and cochlea derived by fluorescence-activated cell sorting (FACS) in the SHIELD (Shared Harvard Inner-Ear Laboratory Database) database [197]. 2 Protein expression of the affected genes in the epidermis as referenced from The Human Protein Atlas (http://www.proteinatlas.org) [198] Abbreviations: F, fibroblasts; K, keratinocytes; L, Langerhans cells; M, melanocytes.

4.1. HHI with Pigment Disorders

Syndromic HHI with pigmentary disorders was found associated with diverse molecular mechanisms, including differentiation and migration of melanocytes, RAS-MAPK signaling, and DNA repair.

4.1.1. Differentiation and Migration of Melanocytes

As mentioned above, certain subtypes of WS type 2, TADS, and COMMAD syndrome can be attributed to pathogenic variants in MITF, while other types of WS are linked to pathogenic variants in PAX3, SNAI2, SOX10, EDNRB, EDN3, and KITLG. These genes are crucial for the differentiation and migration of melanocytes.
The MITF gene on chromosome 3p14.1–p12.3 encodes the protein MITF, which is a basic helix-loop-helix (bHLH)-leucine zipper and plays a role in the development of various cell types, including neural crest-derived melanocytes, optic cup-derived retinal pigment epithelial cells, and melanocytes [199]. In melanocyte differentiation, MITF transactivates the promoter activity of the tyrosinase gene Tyr [200–203]. Thus, pathogenic variants in the MITF gene might lead to absence of melanocytes in the skin, hair, eyes, and stria vascularis of the cochlea. Pax3 and Sox10 encode transcription factors that synergistically regulate the expression of MITF, and pathogenic variants in these two genes also result in pigmentary abnormalities of the hair, skin, and eyes, as well as in SNHL. Specifically, Sox10 activates the MITF pathway by binding onto the MITF promoter. Loss-of-function variants including a 1076delGA in exon 5, a 6-bp insertion in exon 4, along with a tyr83-to-ter variant and a glu189-to-ter variant were found to cause WS type 4C [101]. On the other hand, a ser135-to-thr variant was identified in a patient with WS type 2E [109]. The activation of KitLG-KIT signaling pathway leads to the activation of downstream MITF, and defective KitLG has been linked to WS type 2 [8,9].

Pathogenic variants in Ednrb, the gene encoding the endothelin-B receptor, and those in the gene for its ligand endothelin-3 (Edn3) also result in a lack of melanocytes. Ednrb and Edn3 take part in the migration and proliferation of neural crest-derived cells including melanocytes [204]. Sna2 encodes a zinc finger protein essential to the development of neural crest-derived cells [205]. A pathogenic variant in Slugh, the murine homolog of the human Sna2 gene, causes pigmentary disorders in mice including white forelock and patchy depigmentation over the ventral body, tail, and feet. Hyperactivity and circling behavior observed in Slugh-deficient mice implied the presence of auditory and vestibular dysfunctions. These findings implicate a role for Sna2 in the development and/or migration of neural crest-derived cells [98,106].

4.1.2. RAS-MAPK Signaling

NSML types 1, 2, and 3 result from pathogenic variants in PTPN11, Raf1, and Braf genes, respectively, products of which all participate in the RAS-MAPK signaling cascade. The tyrosine phosphatase encoded by PTPN11 relays signals from cell membrane receptors to cytoplasmic tyrosine kinases and up-regulates the MAPK signaling pathway [206]. The serine/threonine-protein kinase encoded by Raf1 links Ras GTPases to the MAPK/ERK (extracellular signal-regulated kinases) cascade and serves as a decision point leading cells to proliferate, differentiate, or undergo apoptosis. The serine/threonine-protein kinase B-raf, encoded by Braf, facilitates cell membrane-nucleus signaling through phosphorylation of Map2k1 [207,208]. It may further contribute to postsynaptic responses of hippocampal neurons [209].

Histological specimens of lentiginous lesions of NSML cases with pathogenic PTPN11 variants revealed increased numbers of melanocytes and pigments throughout the epidermis, while immunohistochemical studies revealed increased expression levels of endothelin-1 (Et-1), phosphorylated Akt, mTOR, and STAT3 in lentiginous epidermis compared with non-lentiginous skin areas. Higher melanin synthesis rates of human melanoma cells expressing tyrosine-protein phosphatase non-receptor type 11 have been observed in vitro, supporting the link between PTPN11 and hyperpigmentation in NSML patients [210]. Vestibulocochlear anomalies and atrophic cochlear neurons have been observed in patients with pathogenic PTPN11 variants [211].

4.1.3. DNA Repair

XP and CS are caused by defective DNA repair pathways. Defects in Xpc and Xpe, factors in charge of global genome nucleotide excision repair (GG-NER), in Xpa, Xpg, Xpb, and Xpd, which oversee DNA unwinding, as well as in Xpf and Xpg, mediating excision of the damaged nucleotides, lead to hyper- and hypopigmented macules in sun-exposed areas and an increased risk of skin malignancies [212]. Defects in Polh lead to Xpv, a rare subtype of XP.
Increased numbers of melanocytes and elevated melanin levels have been found in skin specimens of freckles from XPC patients. Hyperpigmentation in XP results from increased proliferation and early differentiation of melanocytes due to the mutagenic tendency of cells with impaired GG-NER [21]. UV(ultraviolet)-induced oxidative stress could also induce hyperpigmentation. Melanogenesis is regulated through the ERK signaling pathway activated by mitochondrial reactive oxidative species [213]. The production of UV-induced protective pigments is up-regulated by the mitochondrial protein prohibitin [214,215]. Defective repair mechanisms and UV-induced changes in microenvironment spark apoptotic pathways in XP melanocytes, resulting in hypopigmented areas. Apoptosis of cells in XP patients is triggered by lower doses of UV than needed to induce apoptosis in normal cells [216–219]. Compared to XP, the phenotype of CS includes progeroid appearance, generally without pigmentary changes [220]. XP and CS are associated with SNHI of cochlear origin on audiological assessments. Temporal bone histology at autopsy revealed atrophy of the sensory epithelium and neurons in the cochlea. Atrophies of the stria vascularis, hair cells, or Scarpa’s ganglion have been observed in different cases of XP [133,221].

4.2. HHI with Hyperkeratosis Or Nail Disorders

4.2.1. HHI with Hyperkeratosis

Syndromic HHI with hyperkeratosis are caused by pathogenic variants in two gap junction genes, GJB2 and GJB6, which encode connexins that are key to intercellular signaling [222]. The ectoderm-derived epithelia of the inner ear and the epidermis share the expression of Cx26 and Cx30 [223,224]. In the skin, Cx26 is mainly expressed in the palmoplantar epidermis and the inner and outer root sheaths of the human hair follicle, while Cx30 is predominantly expressed in the differentiated layers of the interfollicular epidermis [225–227]. Defective connexins result in leaky hemichannels and impaired intercellular communication [139,228]. Cx26 plays a role in wound healing and is also involved in the normal differentiation and proliferation of keratinocytes, which may explain the hyperkeratosis observed in individuals with defective Cx26 [228,229].

In the inner ear, connexins are abundantly expressed in the cochlear sensory epithelium, and are key factors in maintaining the potassium levels of the endolymph [20]. Immunohistochemical stainings have revealed that Cx26 and Cx30 are expressed in the spiral limbus, spiral ligament, stria vascularis, and supporting cells of the organ of Corti. Cx26 contributes to normal development of the cochlear sensory epithelium, and compromised inositol 1,4,5-trisphosphate (Ins(1,4,5)P3) permeability of Cx26 has been implicated as a cause of SNHI [230,231]. Additionally, the endocochlear potential generated by the stria vascularis is remarkably disturbed in Cx30-deficient mice [232].

GJB4 encodes Cx30.3, pathogenic variants in which have been linked to erythrokeratodermia variabilis et progressiva, or EKVP [233]. EKVP is a rare, mostly autosomal-dominant genodermatosis featuring erythema gyratum repens and stable hyperkeratotic plaques [234]. How GJB4 variants induce EKVP remains hypothetical. The link between GJB4 and SNHI has not yet been well-established either; however, GJB4 variants have been identified in 11 patients with non-syndromic hearing loss in Taiwan. These patients suffered from congenital bilateral SNHI but no skin lesion was found [235,236]. GJB4 variants have also been identified in Iranian patients with autosomal recessive non-syndromic hearing loss [237,238]. These pilot genotype-phenotype correlation studies serve as the steppingstone to clarify the link between GJB4 and SNHI.

4.2.2. HHI with Nail Disorders

The molecular underpinnings of syndromic HHI with nail disorders involve a plethora of genes related to proton transportation, vesicle transportation, peroxisome function, and hemidesmosomes.

The DDOD-linked ATP6V1B2 gene encodes a component of the vacuolar ATPase for proton transportation. Impaired lysosomal acidification due to V-ATPase deficiency
undermines the Wnt signaling pathway, which is important for normal limb organogenesis. This may explain the dystrophic or atrophic nails present in DDOD patients [239–241]. Immunostaining of mouse cochlea showed predominant expression of Atp6v1b2 in the organ of Corti and spiral ganglion neurons. Consistent with histological findings, auditory brainstem response tests showed elevated hearing thresholds in cochlea-specific Atp6v1b2-knockdown mice, supporting the link between ATP6V1B2 and SNHI [39].

The DOORS-linked TBC1D24 encodes a GTPase-activating protein crucial to vesicle transportation [242,243]. TBC1D24 regulates migration of neural crest cells in coordination with ephrinB2 and the scaffold protein Dishevelled (Dsh) [244]. Immunostaining of mouse cochlea showed predominant expression of Tbc1d24 in inner and outer hair cells, and weaker expression in spiral ganglion neurons [245]. Nails and membranous labyrinth are both ectoderm-derived, which underlies the coexistence of nail dystrophy and SNHI [155].

Heimler syndromes 1 and 2 arise from pathogenic variants in PEX1 and PEX6, respectively, which lead to impaired peroxisome biogenesis [49,52]. Decreased metabolism of very long chain fatty acids underpins the cutaneous findings in the PBD spectrum [45,48]. Reduced or defective peroxisomes in Heimler syndrome patients have been found through immunofluorescence microscopy [51,246]. As oxidative stress is linked to hearing loss, this finding consolidates the relationship between peroxisomal dysfunction and SNHI in Heimler syndrome [49,247,248].

The NPS-related gene LMX1B encodes the LIM homeobox transcription factor, defects in which hinder limb and skin development; the dystrophic nails and orthopedic abnormalities may result from altered embryonic dorsoventral patterning [58,60,61]. Strong expression of the mouse homolog Lmx1b in the hindbrain implies that LMX1B variants disturb inner ear development [249].

The NPEBD-linked CD151 encodes a tetraspan protein crucial to hemidesmosome integrity [63]. CD151 facilitates basement membrane formation, migration of keratinocytes, and adhesion and migration of epithelial cells, highlighting its role in skin integrity and wound healing [250]. Hearing loss has been observed in laminin-deficient mice. As CD151 is key to laminin-binding among other tetraspanin-integrin interactions, defective CD151 may impair normal hearing [251,252].

4.3. HHI with Connective Tissue Disorders

Syndromic HHI with connective tissue disorders result from the deregulation of the extracellular matrix (ECM), dermatan-sulfate (DS) biosynthesis, microtubule assembly, mitochondria-mediated cell death, and inflammatory cascades.

The products of BCS1 and BCS2-associated genes, i.e., zinc finger protein 469 encoded by ZNF469, and PR domain-containing protein 5 encoded by PRDM5, regulate and maintain the ECM [169,253]. Pathogenic variants in PRDM5 lead to decreased or disorganized vital ECM components, including collagen I fibers and decorin, which has been shown in patient-derived fibroblast models [253,254]. Disorganized ECM leads to skin fragility and hyperelasticity in BCS patients [171]. SNHI has been documented in both PRDM5- and ZNF469-associated types of BCS [169,253].

The enzyme products of EDSMC1 and EDSMC2-causing genes CHST14 and dermatan-sulfate epimerase (DSE) are dermatan-4-sulfotransferase-1 (D4ST1) and dermatan-sulfate epimerase, respectively. These enzymes facilitate DS biosynthesis [173,255]. D4ST1 dysfunction hinders normal production and assembly of the ECM. Additionally, disrupted ECM components, including fibronectin and fibrillar collagen types I, III, and V, have been found in D4ST1-deficient patients [74,173]. These ECM defects lead to skin hyperextensibility, easy bruising, increased palmar wrinkling, and propensity to subcutaneous hematoma formation in EDSMC patients [71,173]. EDSMC1 patients with high-tone SNHI have been reported in the literature [72,173]. EDSMC2-causing variants in DSE also result in dysfunctional DS and ECM disarray; however, SNHI has not been reported in EDSMC2 patients [256].
Products of CSCSC1 and CSCSC2-associated genes, i.e., tubulin β chain encoded by TUBB and end-binding protein 2 encoded by MAPRE2, are crucial to microtubule assembly and polymerization [77,78]. Altered MAPRE2 expression perturbs branchial arch patterning, explaining the skin and craniofacial anomalies in CSCSC1 patients [77]. In cochlear sensory cells, microtubules form both dynamic and supporting structures of the organ of Corti [257]. Immunohistochemical staining of the inner ear revealed diffuse expression of β-tubulin, an autoantigen targeted in autoimmune inner ear disease [258–264]. Antibodies recognizing β-tubulin were isolated in the serum of 59% of patients with Meniere’s disease [265]. Taken together, microtubule assembly and dynamics are crucial for maintaining normal hearing.

The product of the MLS gene HCCS is crucial to mitochondrial-mediated apoptosis [175–177]. Defects in this synthase results in a shift from apoptosis to necrosis and induces inflammation and damage to neighboring cells, inducing the cutaneous manifestation of MLS [266].

The CAPS-linked NLRP3 and NLPR12 are mainly expressed in neutrophils and chondrocytes, and gain-of-function variants lead to over-activation of the inflammasome, overstimulation of interleukin (IL)-1β receptors, and overproduction and secretion of IL-1β [185,267,268]. Following the constitutive activation of the NLRP3 inflammasome, mast cells in CAPS patients produce IL-1β, induce neutrophil migration, and promote vascular leakage independent of stimuli [269]. Tissue-resident macrophage/monocyte-like cells reside perivascularly throughout the cochlea [185,270]. NLRP3 inflammasome-induced secretion of IL-1β induces cochlear inflammation, and thus SNHI [271,272]. The recombinant IL-1 receptor antagonist (IL-1Ra) Anakinra ameliorates SNHI, consolidating the role of IL-1β in hearing loss [185,268]. IL-1β also causes higher permeability of cytokines between the perilymph and CSF (cerebrospinal fluid) space via the modiolus, prompting spiral ligament fibrocytes to produce inflammatory mediators [182].

5. Conclusions

Listed in this review is a comprehensive array of syndromic HHI with abnormal cutaneous findings. This provides an outline for clinicians and researchers encountering patients with abnormal manifestations, which are evident in the setting of an outpatient clinic appointment (e.g., in a well-baby clinic). The pathogenesis of the skin manifestations and syndromic HHI of certain syndromes has not yet been fully elucidated. Further molecular and functional studies are necessary to unveil the underlying mechanisms.

Author Contributions: Conceptualization, T.-L.L., C.-C.W.; methodology, T.-L.L., C.-C.W.; writing—original draft preparation, T.-L.L.; writing—review and editing, T.-L.L., P.-H.L., J.-B.H., C.-C.W.; supervision, P.-L.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Morton, C.C.; Nance, W.E. Newborn hearing screening—A silent revolution. N. Engl. J. Med. 2006, 354, 2151–2164. [CrossRef] [PubMed]
2. Hilgert, N.; Smith, R.J.; Van Camp, G. Forty-six genes causing nonsyndromic hearing impairment: Which ones should be analyzed in DNA diagnostics? Mutat. Res. 2009, 681, 189–196. [CrossRef] [PubMed]
3. Azaiez, H.; Booth, K.T.; Ephraim, S.S.; Crone, B.; Black-Ziegelbein, E.A.; Marini, R.J.; Shearer, A.E.; Sloan-Heggen, C.M.; Kolbe, D.; Casavant, T.; et al. Genomic Landscape and Mutational Signatures of Deafness-Associated Genes. Am. J. Hum. Genet. 2018, 103, 484–497. [CrossRef] [PubMed]
4. 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, 391–406. [CrossRef]
5. Read, A.P.; Newton, V.E. Waardenburg syndrome. J. Med. Genet. 1997, 34, 656–665. [CrossRef]
6. Tamayo, M.L.; Gelvez, N.; Rodriguez, M.; Florez, S.; Varon, C.; Medina, D.; Bernal, J.E. Screening program for Waardenburg syndrome in Colombia: Clinical definition and phenotypic variability. Am. J. Med. Genet. A 2008, 146a, 1026–1031. [CrossRef]
7. Hughes, A.E.; Newton, V.E.; Liu, X.Z.; Read, A.P. A gene for Waardenburg syndrome type 2 maps close to the human homologue of the microphthalmia gene at chromosome 3p12-p14.1. Nat. Genet. 1994, 7, 509–512. [CrossRef]
8. Xu, C.; Ren, W.; Zhang, Y.; Zheng, F.; Zhao, H.; Shang, H.; Guo, W.; Yang, S. KIT gene mutation causes deafness and hypopigmentation in Bama miniature pigs. *Am. J. Trans. Res.* 2020, 12, 5095–5107.

9. Zazzo Seco, C.; Serrão de Castro, L.; van Nierop, J.W.; Morin, M.; Jiangiani, S.; Verger, E.J.; Schraders, M.; Maiwald, N.; Wesdorp, M.; Venselaar, H.; 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, 647–660. [CrossRef]

10. Izumi, K.; Kohata, T.; Kimura, Y.; Ishida, S.; Takahashi, T.; Ishiko, A.; Kosaki, K. Tietz syndrome: Unique phenotype specific to mutations of MITF nuclear localization signal. *Clin. Genet.* 2008, 74, 93–95. [CrossRef]

11. George, A.; Zand, D.J.; Hufnagel, R.B.; Sharma, R.; Sergeev, Y.V.; Legare, J.M.; Rice, G.M.; Scott Schwoerer, J.A.; Rius, M.; Tetri, L.; et al. Biallelic Mutations in MITF Cause Coloboma, Osteopetrosis, Microphthalmia, Macrocephaly, Albinism, and Deafness. *Am. J. Hum. Genet.* 2016, 99, 1388–1394. [CrossRef] [PubMed]

12. Morgan, N.V.; Morris, M.R.; Cangul, H.; Gleeson, D.; Straatman-Iwanowska, A.; Davies, N.; Keenan, S.; Pasha, S.; Rahman, F.; Gentle, D.; et al. Mutations in SLC2A9, encoding an equilibrative nucleoside transporter ENT3, cause a familial histiocytosis syndrome (Faisalabad histiocytosis) and familial Rosai-Dorfman disease. *PloS Genet.* 2010, 6, e1000833. [CrossRef] [PubMed]

13. Gorlin, R.J.; Anderson, R.C.; Blaw, M. Multiple lentigenes syndrome. *Am. J. Dis. Child.* (1960) 1969, 117, 652–662. [CrossRef] [PubMed]

14. Sarkozy, A.; Carta, C.; Moretti, S.; Zampino, G.; Digilio, M.C.; Pantaleoni, F.; Scoiello, A.P.; Esposito, G.; Cordeddu, V.; Lepri, F.; et al. Germline BRAF mutations in Noonan, LEOPARD, and cardiofaciocutaneous syndromes: Molecular diversity and associated phenotypic spectrum. *Hum. Mutat.* 2009, 30, 695–702. [CrossRef] [PubMed]

15. Sarkozy, A.; Digilio, M.C.; Dallapiccola, B. Leopard syndrome. *Orphanet J. Rare Dis.* 2008, 3, 13. [CrossRef] [PubMed]

16. Digilio, M.C.; Sarkozy, A.; de Zorzi, A.; Pacileo, G.; Limongelli, G.; Mingarelli, R.; Calabro, R.; Marino, B.; Dallapiccola, B. LEOPARD syndrome: Clinical diagnosis in the first year of life. *Am. J. Med. Genet. A* 2006, 140, 740–746. [CrossRef] [PubMed]

17. Jin, Y.; Birlea, S.A.; Fain, P.R.; Gowan, K.; Riccardi, S.L.; Hollander, P.J.; Mailloux, C.M.; Sufit, A.J.D.; Hutton, S.M.; Amadi-Myers, A.; et al. Variant of TYR and Autoimmunity Susceptibility Loci in Generalized Vitiligo. *N. Engl. J. Med.* 2010, 362, 1686–1697. [CrossRef]

18. Cleaver, J.E. Do we know the cause of xeroderma pigmentosum? *Carcinogenesis* 1990, 11, 875–882. [CrossRef]

19. Kashiyama, K.; Nakazawa, Y.; Pilaz, D.T.; Guo, C.; Shimada, M.; Sasaki, K.; Fawcett, H.; Wing, J.F.; Lewin, S.O.; Carr, L.; et al. Novel XPG (ERCC5) mutations affect DNA repair and cell survival after ultraviolet but not oxidative stress. *Am. J. Hum. Genet.* 2013, 92, 807–819. [CrossRef]

20. Soltys, D.T.; Rocha, C.R.; Lerner, L.K.; de Souza, T.A.; Munford, V.; Cabral, F.; Nardo, T.; Stefanini, M.; Sarasin, A.; Cabral-Neto, J.B.; et al. Mutations in SLC29A3, encoding an equilibrative nucleoside transporter ENT3, cause a familial histiocytosis syndrome (Faisalabad histiocytosis) and familial Rosai-Dorfman disease. *Am. J. Med. Genet. A* 2013, 34, 481–489. [CrossRef]

21. Kasraian, Z.; Trompeziński, S.; Cario-André, M.; Morice-Picard, F.; Ged, C.; Jullie, M.L.; Taieb, A.; Rezvani, H.R. Pigmentation abnormalities in nucleotide excision repair disorders: Evidence and hypotheses. *Pigment. Cell Melanoma Res.* 2019, 32, 25–40. [CrossRef]

22. Nance, M.A.; Berry, S.A. Cockayne syndrome: Review of 140 cases. *Am. J. Med. Genet.* 1992, 42, 68–84. [CrossRef] [PubMed]

23. Mallory, D.L.; Tanganelli, B.; Colella, S.; Steingrimsdottir, H.; van Gool, A.J.; Troelstra, C.; Stefanini, M.; Lehmann, A.R. Molecular analysis of mutations in the CSB (ERCC6) gene in patients with Cockayne syndrome. *Am. J. Med. Genet. A* 2009, 147, 1442–1449. [CrossRef] [PubMed]

24. Rapin, I.; Lindenbaum, Y.; Dickson, D.W.; Kraemer, K.H.; Robbins, J.H. Cockayne syndrome and xeroderma pigmentosum. *Neurology* 2000, 55, 1442–1449. [CrossRef]

25. Licht, C.L.; Stevnsner, T.; Bohr, V.A. Cockayne syndrome group B cellular and biochemical functions. *Am. J. Hum. Genet.* 2003, 73, 1217–1239. [CrossRef]

26. Verbov, J. Palmoplantar keratoderma, deafness and atopy. *Br. J. Dermatol.* 1987, 116, 881–882. [CrossRef]

27. Heathcote, C.; Syrris, P.; Carter, N.D.; Patton, M.A. A connexin 26 mutation causes a syndrome of sensorineural hearing loss and palmoplantar hyperkeratosis (MIM 148350). *J. Med. Genet.* 2000, 37, 50–51. [CrossRef]

28. Maestrini, E.; Korge, B.P.; Ocaña-Sierra, J.; Calzolari, E.; Cambiaghi, S.; Scudder, P.M.; Hovanian, A.; Monaco, A.P.; Munro, C.S. A missense mutation in connexin26, D66H, causes mutilating keratoderma with sensorineural deafness (Vohwinkel’s syndrome) in three unrelated families. *Hum. Mol. Genet.* 1999, 8, 1237–1243. [CrossRef]

29. Sensi, A.; Bettoli, V.; Zampino, M.R.; Gandini, E.; Calzolari, E. Vohwinkel syndrome (mutilating keratoderma) associated with craniofacial anomalies. *Am. J. Med. Genet.* 1994, 50, 201–203. [CrossRef]

30. De Zwart-Storm, E.A.; van Geel, M.; Veysey, E.; Burge, S.; Cooper, S.; Steijlen, P.M.; Martin, P.E.; van Steensel, M.A. A novel missense mutation in GJB2, p.Tyr65His, causes severe Vohwinkel syndrome. *Br. J. Dermatol.* 2011, 164, 197–199. [CrossRef]

31. Richard, G.; Brown, N.; Ishida-Yamamoto, A.; Krol, A. Expanding the phenotypic spectrum of Cx26 disorders: Bart-Pumphrey syndrome is caused by a novel missense mutation in GJB2. *J. Investig. Dermatol.* 2004, 123, 856–863. [CrossRef] [PubMed]

32. Alexandrino, F.; Sartorato, E.L.; Marques-de-Faria, A.P.; Steiner, C.E. G59S mutation in the GJB2 (connexin 26) gene in a patient with Bart-Pumphrey syndrome. *Am. J. Med. Genet. A* 2005, 136, 282–284. [CrossRef] [PubMed]

33. Bart, R.S.; Pumphrey, R.E. Knuckle pads, leukonychia and deafness. A dominantly inherited syndrome. *N. Engl. J. Med.* 1967, 276, 202–207. [CrossRef] [PubMed]
34. Van Geel, M.; van Steensel, M.A.; Küster, W.; Hennies, H.C.; Happle, R.; Steijlen, P.M.; König, A. HID and KID syndromes are associated with the same connexin 26 mutation. Br. J. Dermatol. 2002, 146, 938–942. [CrossRef] [PubMed]

35. Baden, H.P.; Bronstein, B.R. Ichthyosiform dermatosis and deafness. Report of a case and review of the literature. Arch. Dermatol. 1988, 124, 102–106. [CrossRef] [PubMed]

36. Grob, J.J.; Breton, A.; Bonafe, J.L.; Sauvan-Ferdani, M.; Bonerandi, J.J. Keratitis, ichthyosis, and deafness (KID) syndrome. Vertical transmission and death from multiple squamous cell carcinomas. Arch. Dermatol. 1987, 123, 777–782. [CrossRef]

37. Mikaelian, D.O.; Der Kaloustian, V.M.; Shahin, N.A.; Barsoumian, V.M. Congenital Ectodermal Dysplasia with Hearing Loss. Arch. Otolaryngol. 1970, 92, 85–89. [CrossRef]

38. Kondoh, T.; Tsuru, A.; Matsumoto, T.; Matsuoka, T.; Tsuji, Y. Autosomal dominant onychodystrophy and congenital sensorineural deafness. J. Hum. Genet. 1999, 44, 60–62. [CrossRef]

39. Yuan, Y.; Zhang, J.; Chang, Q.; Zeng, J.; Xin, F.; Wang, J.; Zhu, Q.; Wu, J.; Lu, J.; Guo, W.; et al. De novo mutation in ATP6V1B2 impairs lysosome acidification and causes dominant deafness-onychodystrophy syndrome. Cell Res. 2014, 24, 1370–1373. [CrossRef]

40. Menendez, I.; Carranza, C.; Herrera, M.; Marroquin, J.; Foster, J., 2nd; Cengiz, F.B.; Bademci, G.; Tekin, M. Dominant deafness-onychodystrophy caused by an ATP6V1B2 mutation. Clin. Case Rep. 2017, 5, 376–379. [CrossRef]

41. James, A.W.; Miranda, S.G.; Culver, K.; Hall, B.D.; Golabi, M. DOOR syndrome: Clinical report, literature review and discussion of natural history. Am. J. Med. Genet. A 2007, 143A, 2821–2831. [CrossRef] [PubMed]

42. Afawi, Z.; Mandelstam, S.; Korczyn, A.D.; Kivity, S.; Wald, S.; Shalata, A.; Oliver, K.L.; Corbett, M.; Gecc, J.; Berkovic, S.F.; et al. TBC1D24 mutation associated with focal epilepsy, cognitive impairment and a distinctive cerebro-cerebellar malformation. Epilepsy Res. 2013, 105, 240–244. [CrossRef] [PubMed]

43. Campeau, P.M.; Kaspersavicute, D.; Lu, J.T.; Burrage, L.C.; Kim, C.; Hori, M.; Powell, B.R.; Stewart, F.; Félix, T.M.; van den Ende, J.; et al. The genetic basis of DOORS syndrome: An exome-sequencing study. Lancet Neurol. 2014, 13, 44–58. [CrossRef]

44. Lüthy, K.; Mei, D.; Fischer, B.; De Fusco, M.; Swerts, J.; Paesmans, J.; Parrini, E.; Lubarr, N.; Meijer, I.A.; Mackenzie, K.M.; et al. TBC1D24-TLDc-related epilepsy exercise-induced dystonia: Rescue by antioxidants in a disease model. Brain 2019, 142, 2319–2335. [CrossRef] [PubMed]

45. Moser, H.W. Genotype-phenotype correlations in disorders of peroxisome biogenesis. Mol. Genet. Metab. 1999, 68, 316–327. [CrossRef]

46. Crane, D.I.; Maxwell, M.A.; Paton, B.C. PEX1 mutations in the Zellweger spectrum of the peroxisome biogenesis disorders. Hum. Mutat. 2005, 26, 167–175. [CrossRef]

47. Ong, K.R.; Visram, S.; McKaig, S.; Brueton, L.A. Sensorineural deafness, enamel abnormalities and nail abnormalities: A case report of Heimler syndrome in identical twin girls. Eur. J. Med. Genet. 2006, 49, 187–193. [CrossRef]

48. Chen, H.; Liu, Z.; Huang, X. Drosophila models of peroxisomal biogenesis disorder: Peroxins are required for spermatogenesis and very-long-chain fatty acid metabolism. Human Mol. Genet. 2009, 19, 494–505. [CrossRef]

49. Smith, J.J.; Atchison, J.D. Peroxisomes take shape. Nat. Rev. Mol. Cell Biol. 2013, 14, 803–817. [CrossRef]

50. Fujiy, Y.; Okamoto, K.; Mukai, S.; Honsho, M.; Tamura, S. Peroxisome biogenesis in mammalian cells. Front. Physiol. 2014, 5, 307. [CrossRef]

51. Ratbi, I.; Falkenberg, K.D.; Sommen, M.; Al-Sheqaih, N.; Guaoua, S.; Vandeweyer, G.; Uerquhart, J.E.; Chandler, K.E.; Williams, S.G.; Roberts, N.A.; et al. Heimler Syndrome Is Caused by Hypomorphic Mutations in the Peroxisome-Biogenesis Genes PEX1 and PEX6. Am. J. Hum. Genet. 2015, 97, 535–545. [CrossRef]

52. Grim, I.; Erdmann, R.; Girzalsky, W. Role of AAA+-proteins in peroxisome biogenesis and function. Biochim. Biophys. Acta (BBA) Mol. Cell Res. 2016, 1863, 828–837. [CrossRef] [PubMed]

53. Falkenberg, K.D.; Braverman, N.E.; Moser, A.B.; Steinberg, S.J.; Klouwer, F.C.C.; Schlüter, A.; Ruiz, M.; Pujol, A.; Engvall, M.; Naess, K.; et al. Allelic Expression Imbalance Promoting a Mutant PEX6 Allele Causes Zellweger Spectrum Disorder. Am. J. Hum. Genet. 2017, 101, 965–976. [CrossRef]

54. Schieferdecker, A.; Wendler, P. Structural Mapping of Missense Mutations in the Pex1/Pex6 Complex. Int. J. Mol. Sci. 2019, 20, 3756. [CrossRef]

55. Yu, H.-L.; Shen, Y.; Sun, Y.-M.; Zhang, Y. Two novel mutations of PEX6 in one Chinese Zellweger spectrum disorder and their clinical characteristics. Ann Transl. Med. 2019, 7, 5. [CrossRef]

56. Hawkins, C.F.; Smith, O.E. Renal dysplasia in a family with multiple hereditary abnormalities including iliac horns. Lancet (Lond. Engl.) 1950, I, 803–808. [CrossRef]

57. Dreyer, S.D.; Zhou, G.; Baldini, A.; Winterpacht, A.; Zabel, B.; Cole, W.; Johnson, R.L.; Lee, B. Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. Nat. Genet. 1998, 19, 47–50. [CrossRef]

58. Ding, Y.Q.; Yin, J.; Kania, A.; Zhao, Z.Q.; Johnson, R.L.; Chen, Z.F. Lmx1b controls the differentiation and migration of the superficial dorsal horn neurons of the spinal cord. Development 2004, 131, 3693–3703. [CrossRef]

59. Bongers, E.M.; Huysmans, F.T.; Levchenko, E.; de Rooy, J.W.; Blickman, J.G.; Admiral, R.J.; Huygen, P.L.; Cruyssen, J.R.; Toolens, P.A.; Prins, J.B.; et al. Genotype-phenotype studies in nail-patella syndrome show that LMX1B mutation location is involved in the risk of developing nephropathy. Eur. J. Hum. Genet. 2005, 13, 935–946. [CrossRef]

60. Dai, J.X.; Johnson, R.L.; Ding, Y.Q. Manifold functions of the Nail-Patella Syndrome gene Lmx1b in vertebrate development. Dev. Growth Differ. 2009, 51, 241–250. [CrossRef]
61. Feenstra, J.M.; Kanaya, K.; Pira, C.U.; Hoffman, S.E.; Eppey, R.J.; Oberg, K.C. Detection of genes regulated by Lmx1b during limb dorsalisitization. Dev. Growth Differ. 2012, 54, 451–462. [CrossRef] [PubMed]

62. Kagan, A.; Feld, S.; Chemke, J.; Bar-Khayim, Y. Occurrence of hereditary nephritis, pretibial epidermolysis bullosa and β-thalassemia minor in two siblings with end-stage renal disease. Nephron 1988, 49, 331–332. [CrossRef] [PubMed]

63. Sterk, L.M.; Geuijen, C.A.; Oomen, L.C.; Calafat, J.; Janssen, H.; Sonnenberg, A. The tetraspan molecule CD151, a novel constituent of hemidesmosomes, associates with the integrin α6β4 and may regulate the spatial organization of hemidesmosomes. J. Cell Biol. 2000, 149, 969–982. [CrossRef] [PubMed]

64. Karamatic Crew, V.; Burton, N.; Kagan, A.; Green, C.A.; Levene, C.; Flinter, F.; Brady, R.L.; Daniels, G.; Anstee, D.J. CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin. Blood 2004, 104, 2217–2223. [CrossRef]

65. Reimer, A.; He, Y.; Has, C. Update on Genetic Conditions Affecting the Skin and the Kidneys. Front. Pediatrics 2018, 6, 43. [CrossRef]

66. Al-Hussain, H.; Zeisberger, S.M.; Huber, P.R.; Giunta, C.; Steinmann, B. Brittle cornea syndrome and its delineation from the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS VI): Report on 23 patients and review of the literature. Am. J. Med. Genet. A 2004, 124, 28–34. [CrossRef]

67. Malfait, F.; Francanomo, C.; Byers, P.; Belmont, J.; Berglund, B.; Black, J.; Bloom, L.; Bowen, J.M.; Brady, A.F.; Burrows, N.P.; et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am. J. Med. Genet. C Semin. Med. Genet. 2017, 175, 8–26. [CrossRef]

68. Bertelsen, T.I. Dysgenesis mesodermalis corneae et sclerae. Rupture of both corneae in a patient with blue sclerae. Acta Ophthalmol. (Copenh) 1968, 46, 486–491. [CrossRef]

69. Porter, L.F.; Galli, G.G.; Williamson, S.; Selley, J.; Knight, D.; Elcioglu, N.; Aydin, A.; Elcioglu, M.; Venselaar, H.; Lund, A.H.; et al. A role for repressive complexes and H3K9 di-methylation in PRDM5-associated brittle cornea syndrome. Hum. Mol. Genet. 2015, 24, 6565–6579. [CrossRef]

70. Cameron, J.A. Corneal abnormalities in Ehlers-Danlos syndrome type VI. Cornea 1993, 12, 54–59. [CrossRef]

71. Steinmann, B.; Gitzelmann, R.; Vogel, A.; Grant, M.E.; Harwood, R.; Hear, C.H. Ehlers-Danlos syndrome in two siblings with defective lysyl hydroxylase activity in cultured skin fibroblasts but only mild hydroxylysine deficit in skin. Herts. Paediatr. Acta 1975, 30, 255–274. [PubMed]

72. Kosho, T.; Miyake, N.; Hatamochi, A.; Takahashi, J.; Kato, H.; Miyahara, T.; Igawa, Y.; Yasui, H.; Ishida, T.; Ono, K.; et al. A new Ehlers-Danlos syndrome with craniofacial characteristics, multiple congenital contractures, progressive joint and skin laxity, and multisystem fragility-related manifestations. Am. J. Med. Genet. A 2010, 152, 1333–1346. [CrossRef] [PubMed]

73. Malfait, F.; Sxy, D.; Vlumens, P.; Symoens, S.; Nampoorthi, S.; Hermanns-Lê, T.; Van Laer, L.; De Paepe, A. Musculocontractural Ehlers-Danlos Syndrome (former EDS type VIB) and adducted thumb clubfoot syndrome (ATCS) represent a single clinical entity caused by mutations in the dermatan-4-sulfotransferase 1 encoding CHST14 gene. Hum. Mutat. 2010, 31, 1233–1239. [CrossRef] [PubMed]

74. Janecke, A.R.; Li, B.; Boehm, M.; Krabichler, B.; Rohrbach, M.; Müller, T.; Fuchs, I.; Golas, G.; Katagiri, Y.; Ziegler, S.G.; et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am. J. Med. Genet. A 2016, 170a, 103–115. [CrossRef] [PubMed]

75. Beighton, P.; De Paepe, A.; Steinmann, B.; Tsipouras, P.; Wenstrup, R.J. Ehlers-Danlos syndromes: Revised nosology, Villefranche, 1998. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am. J. Med. Genet. 1998, 77, 31–37. [CrossRef]

76. Kunze, J.; Reihm, H. A new genetic disorder: Autosomal-dominant multiple benign ring-shaped skin creases. Eur. J. Pediatrics 1982, 138, 301–303. [CrossRef]

77. Isrie, M.; Breuss, M.; Tian, G.; Hansen, A.H.; Cristofoli, F.; Morandell, J.; Kupchinsky, Z.A.; Sofrim, A.; Rodriguez-Rodriguez, C.M.; Dapena, E.P.; et al. Mutations in Either TUBB or MAPRE2 Cause Circumferential Skin Creases Kunze Type. J. Med. Genet. 2015, 104, 2217–2223. [CrossRef]

78. Tinsa, F.; Aissa, K.; Meddeeb, M.; Bousnina, D.; Boussetta, K.; Bousnina, S. Multiple congenital anomalies/mental retardation syndrome with multiple circumferential skin creases: A new syndrome? J. Child. Neurol. 2009, 24, 224–227. [CrossRef]

79. Wouters, L.; Rodriguez Rodriguez, C.M.; Dapena, E.P.; Poorten, V.V.; Devriendt, K.; Van Esch, H. Circumferential skin creases, cleft palate, typical face, intellectual disability and growth delay: “circumferential skin creases Kunze type”. Eur. J. Med. Genet. 2011, 54, 236–240. [CrossRef]

80. Lindsay, E.A.; Grillo, A.; Ferrero, G.B.; Roth, E.J.; Magnes, E.; Grompe, M.; Hultén, M.; Gould, C.; Baldini, A.; Zoghbi, H.Y.; et al. Microphthalmia with linear skin defects (MLS) syndrome: Clinical, cytogenetic, and molecular characterization. Am. J. Med. Genet. 1993, 486–491. [CrossRef] [PubMed]

81. Al-Gazali, L.I.; Mueller, R.F.; Caine, A.; Antoniou, A.; McCartney, A.; Fitchett, M.; Dennis, N.R. Two 46,XX,t(X;Y) females with linear skin defects and a novel congenital microphthalmia: A new microphthalmia syndrome at Xp22.3. J. Med. Genet. 1990, 27, 59–63. [CrossRef] [PubMed]
83. Happle, R.; Daniëls, O.; Koopman, R.J. MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea): An X-linked phenotype distinct from Goltz syndrome. Am. J. Med. Genet. 1993, 47, 710–713. [CrossRef] [PubMed]

84. Kile, R.L.; Rusk, H.A. A Case of Cold Urticaria with an Unusual Family History. J. Am. Med. Assoc. 1940, 114, 1067–1068. [CrossRef]

85. Zip, C.M.; Ross, J.B.; Greaves, M.W.; Scriver, C.R.; Mitchell, J.J.; Zoar, S. Familial cold urticaria. Clin. Exp. Dermatol. 1993, 18, 338–341. [CrossRef]

86. Jérémie, F.; Duquesnoy, P.; Fernandes-Alnemri, T.; Cochet, E.; Yu, J.W.; Lackmy-Port-Lis, M.; Grimpel, E.; Landman-Parker, J.; Hentgen, V.; Marlin, S.; et al. Mutations in NALP12 cause hereditary periodic fever syndromes. Proc. Natl. Acad. Sci. U.S.A. 2008, 105, 1614–1619. [CrossRef]

87. Borghini, S.; Tassi, S.; Chiesa, S.; Caroli, F.; Carta, S.; Caorsi, R.; Fiore, M.; Delfino, L.; Lasigià, D.; Ferraris, C.; et al. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheum. 2011, 63, 830–839. [CrossRef]

88. Shen, M.; Tang, L.; Shi, X.; Zeng, X.; Yao, Q. NLRP12 autoinflammatory disease: A Chinese case series and literature review. Clin. Rheumatol. 2017, 36, 1661–1667. [CrossRef]

89. Muckle, T.J.; Wells, M. Urticaria, deafness, and amyloidosis: A new heredo-familial syndrome. Q. J. Med. 1962, 31, 235–248.

90. Hoffman, H.M.; Mueller, J.L.; Broide, D.H.; Wanderer, A.A.; Kolodner, R.D. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat. Genet. 2001, 29, 301–305. [CrossRef]

91. Dodé, C.; Le Dû, N.; Cuisset, L.; Letourneur, E.; Berthelot, J.M.; Vaudour, G.; Meyrier, A.; Watts, R.A.; Scott, D.G.; Nicholls, A.; et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: A novel mutation underlies both syndromes. Am. J. Hum. Genet. 2002, 70, 1498–1506. [CrossRef] [PubMed]

92. Prieur, A.M. A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. Clin. Exp. Rheumatol. 2001, 19, 103–106. [PubMed]

93. Boschan, C.; Witt, O.; Lohse, P.; Földvari, I.; Zappel, H.; Schweigerer, L. Neonatal-onset multisystem inflammatory disease (NOMID) due to a novel S331R mutation of the CIAS1 gene and response to interleukin-1 receptor antagonist treatment. Am. J. Med. Genet. A 2006, 140, 883–886. [CrossRef] [PubMed]

94. Aksentijevich, I.; Nowak, M.; Mallah, M.; Chae, J.J.; Watford, W.T.; Hofmann, S.R.; Stein, L.; Russo, R.; Goldsmith, D.; Dent, P.; et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): A new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheum. 2002, 46, 3340–3348. [CrossRef] [PubMed]

95. Feldmann, J.; Prieur, A.M.; Quartier, P.; Berquin, P.; Certain, S.; Cortis, E.; Teillac-Hamel, D.; Fischer, A.; de Saint Basile, G. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am. J. Hum. Genet. 2002, 71, 198–203. [CrossRef] [PubMed]

96. Boyle, M.I.; Jespersgaard, C.; Brondum-Nielsen, K.; Bisgaard, A.M.; Tumer, Z. Cornelia de Lange syndrome. Clin. Genet. 2015, 88, 1–12. [CrossRef]

97. Song, J.; Feng, Y.; Acke, F.R.; Coucke, P.; Vleminckx, K.; Dhooge, I.J. Hearing loss in Waardenburg syndrome: A systematic review. Clin. Genet. 2016, 89, 416–425. [CrossRef]

98. Tassabehji, M.; Newton, V.E.; Read, A.P. Waardenburg syndrome type 2 caused by mutations in the human microphthalmia (MITF) gene. Nat. Genet. 1994, 8, 251–255. [CrossRef]

99. Klein, D. Historical background and evidence for dominant inheritance of the Klein-Waardenburg syndrome (type III). Am. J. Med. Genet. 1983, 14, 231–239. [PubMed]

100. Waardenburg, P.J. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with congenital deafness. Am. J. Hum. Genet. 1951, 3, 195–253.

101. Pingault, V.; Bonduard, N.; Kuhlbrodt, K.; Goerich, D.E.; Préhu, M.O.; Puliti, A.; Herbarth, B.; Hermans-Borgmeyer, I.; Legius, E.; Matthijs, G.; et al. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat. Genet. 1998, 18, 171–173. [CrossRef] [PubMed]

102. Bonduard, N.; Dastot-Le Moal, L.; Chastina, L.; Collot, N.; Baral, V.; Marlin, S.; Attie-Bitach, T.; Giurgea, I.; Skopinski, L.; Reardon, W.; et al. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. Am. J. Hum. Genet. 2007, 81, 1169–1185. [CrossRef] [PubMed]

103. Edery, P.; Attié, T.; Amiel, J.; Pelet, A.; Eng, C.; Hofstra, R.M.; Martelli, H.; Bidaud, C.; Munnich, A.; Lyonnet, S. Mutation of the endothelin-3 gene in the Waardenburg-Hirschsprung disease (Shah-Waardenburg syndrome). Nat. Genet. 1996, 12, 442–444. [CrossRef] [PubMed]

104. Hofstra, R.M.W.; Oisinga, J.; Tan-Sindhunata, G.; Wu, Y.; Kamsteeg, E.-J.; Stulp, R.P.; van Ravenswaaij-Arts, C.; Majoor-Krakauer, D.; Angrist, M.; Chakravarti, A.; 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, 445–447. [CrossRef] [PubMed]

105. Inoue, K.; Khajavi, M.; Ohyama, T.; Hirabayashi, S.; Wilson, J.; Reggin, J.D.; Mancias, P.; Butler, I.J.; Wilkinson, M.F.; Wegner, M.; et al. Molecular mechanism for distinct neurological phenotypes conveyed by allelic truncating mutations. Nat. Genet. 2004, 36, 361–369. [CrossRef] [PubMed]

106. Sánchez-Martin, M.; Rodriguez-García, A.; Pérez-Losada, J.; Sagrera, A.; Read, A.P.; Sánchez-Garcia, I. SLUG (SNAI2) deletions in patients with Waardenburg disease. Hum. Mol. Genet. 2002, 11, 3231–3236. [CrossRef]
Tachibana, M. MITF: A Stream Flowing for Pigment Cells. *Pigment. Cell Res.* 2000, 13, 230–240. [CrossRef]

Bard, L.A. Heterogeneity in Waardenburg’s syndrome. Report of a family with ocular albinism. *Arch. Ophthalmol. (Chic. Ill. 1960) 1978*, 86, 1193–1198. [CrossRef]

Bondurand, N.; Pingault, V.; Goerich, D.E.; Lemort, N.; Sock, E.; Caignec, C.L.; Wegner, M.; Goossens, M. Interaction among SOX10, PAX3 and MITF; three genes altered in Waardenburg syndrome. *Human Mol. Genet.* 2000, 9, 1907–1917. [CrossRef]

Gross, A.; Kunze, J.; Maier, R.F.; Stollenburg-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, 322–326. [CrossRef]

Verheij, J.B.; Kunze, J.; Osinga, J.; van Essen, A.J.; Hofstra, R.M. ABCD syndrome is caused by a homozygous mutation in the EDNRB gene. *Am. J. Med. Genet.* 2002, 108, 223–225. [CrossRef]

Bondurand, N.; Southard-Smith, E.M. Mouse models of Hirschsprung disease and other developmental disorders of the enteric nervous system: Old and new players. *Dev. Biol.* 2016, 417, 139–157. [CrossRef]

Tietz, W. A syndrome of deaf-mutism associated with albinism showing dominant autosomal inheritance. *Am. J. Hum. Genet.* 1963, 15, 259–264. [PubMed]

Smith, S.D.; Kelley, P.M.; Kenyon, J.B.; Hoover, D. Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF. *J. Med. Genet.* 2000, 37, 446–448. [CrossRef] [PubMed]

Takebayashi, K.; Chida, K.; Tsukamoto, I.; Morii, E.; Munakata, H.; Arnheiter, H.; Kuroki, T.; Kitamura, Y.; Nomura, S. The recessive phenotype displayed by a dominant negative microphthalmia-associated transcription factor mutant is a result of impaired nuclear potential. *Mol. Cell. Biol.* 1996, 16, 1203–1211. [CrossRef] [PubMed]

Molho-Pessach, V.; Agha, Z.; Aamar, S.; Glaser, B.; Doviner, V.; Hiller, N.; Zangen, D.H.; Raas-Rothschild, A.; Ben-Neriah, Z.; Shweiki, S.; et al. The H Syndrome: A genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin with systemic manifestations. *J. Am. Acad. Dermatol.* 2008, 59, 79–85. [CrossRef]

Jaouadi, H.; Zaouak, A.; Sellami, K.; Messaoud, O.; Chargui, M.; Hammami, H.; Jones, M.; Jouini, R.; Chadi Debbiche, A.; Chraiet, K.; et al. H syndrome: Clinical, histological and genetic investigation in Tunisian patients. *J. Dermatol.* 2018, 45, 978–985. [CrossRef]

Jonard, L.; Coulouignier, V.; Pierrot, S.; Louha, M.; Gherbi, S.; Denoyelle, F.; Marlin, S. Progressive hearing loss associated with a unique cervical node due to a homozygous SLC29A3 mutation: A very mild phenotype. *Eur. J. Med. Genet.* 2012, 55, 56–58. [CrossRef] [PubMed]

Baldwin, S.A.; Yao, S.Y.; Hyde, R.J.; Ng, A.M.; Foppolo, S.; Barnes, K.; Ritzel, M.W.; Cass, C.E.; Young, J.D. Functional characterization of novel human and mouse equilibrative nucleoside transporters (hENT3 and mENT3) located in intracellular membranes. *J. Biol. Chem.* 2005, 280, 15880–15887. [CrossRef]

Digilio, M.C.; Conti, E.; Sarkozy, A.; Mingarelli, R.; Dottorini, T.; Marino, B.; Pizzuti, A.; Dallapiccola, B. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes with PTEN11 gene. *Am. J. Hum. Genet.* 2002, 71, 389–394. [CrossRef]

Kim, J.; Kim, M.R.; Kim, H.J.; Lee, K.A.; Lee, M.G. LEOPARD Syndrome with PTEN11 Gene Mutation Showing Six Cardinal Symptoms of LEOPARD. *Ann. Dermatol.* 2011, 23, 223–235. [CrossRef] [PubMed]

Roberts, A.E.; Allanson, J.E.; Tartaglia, M.; Gelb, B.D. Noonan syndrome. *Lancet (Lond. Engl.)* 2013, 381, 333–342. [CrossRef]

El Bouchikhi, I.; Belhassan, K.; Moufif, F.Z.; Iraqui Houssaini, M.; Bouguenouch, L.; Sami, I.; Atmani, S.; Ould, K. Noonan syndrome-causing genes: Molecular update and an assessment of the mutation rate. *Int. J. Pediatrics Adolesc. Med.* 2016, 3, 133–142. [CrossRef] [PubMed]

Bader, P.I.; Biegel, A.; Epinette, W.W.; Nance, W.E. Vitiligo and dysgammaglobulinemia. A case report and family study. *Clin. Genet.* 1975, 7, 62–76. [CrossRef]

Jin, Y.; Mailoux, C.M.; Gowen, K.; Riccardi, S.L.; LaBerge, G.; Bennett, D.C.; Fain, P.R.; Spritz, R.A. NALP1 in vitiligo-associated multiple autoimmune disease. *N. Engl. J. Med.* 2007, 356, 1216–1225. [CrossRef]

Goudie, R.B.; Goudie, D.R.; Dick, H.M.; Ferguson-Smith, M.A. Unstable mutations in vitiligo, organ-specific autoimmune diseases, and multiple endocrine adenoma/peptic-ulcer syndrome. *Lancet (Lond. Engl.)* 1980, 2, 285–287. [CrossRef]

Damico, F.M.; Cunha-Neto, E.; Goldberg, A.C.; Iwai, L.K.; Marin, M.L.; Hammer, J.; Kalil, Y.; Yamamoto, J.H. T-cell recognition and cytokine profile induced by melanocyte epitopes in patients with HLA-DRB1*0405-positive and -negative Vogt-Koyanagi-Harada uveitis. *Investig. Ophthalmol. Vis. Sci.* 2005, 46, 2465–2471. [CrossRef]

Sugita, S.; Takase, H.; Taguchi, C.; Imai, Y.; Kamoi, K.; Kawaguchi, T.; Sugamoto, Y.; Futagami, Y.; Itoh, K.; Mochizuki, M. Ocular infiltrating CD4+ T cells from patients with Vogt-Koyanagi-Harada disease recognize human melanocyte antigens. *Investig. Ophthalmol. Vis. Sci.* 2006, 47, 2547–2554. [CrossRef] [PubMed]

Karikkineth, A.C.; Scheibye-Knudsen, M.; Fivenson, E.; Croteau, D.L.; Bohr, V.A. Cockayne syndrome: Clinical features, model systems and pathways. *Ageing Res. Rev.* 2017, 33, 3–17. [CrossRef]

Oh, K.S.; Khan, S.G.; Jaspers, N.G.; Raams, A.; Ueda, T.; Lehmann, A.; Friedmann, P.S.; Emmert, S.; Gratchev, A.; Lachlan, K.; et al. Phenotypic heterogeneity in the XPB DNA helicase gene (ERCC3): Xeroderma pigmentosum without and with Cockayne syndrome. *Hum. Mutat.* 2006, 27, 1092–1103. [CrossRef]

Hirai, Y.; Kodama, Y.; Moriwaki, S.; Noda, A.; Cullings, H.M.; Macphee, D.G.; Kodama, K.; Mabuchi, K.; Kraemer, K.H.; Land, C.E.; et al. Heterozygous individuals bearing a founder mutation in the XPA DNA repair gene comprise nearly 1% of the Japanese population. *Mutat. Res.* 2006, 601, 171–178. [CrossRef] [PubMed]
181. Kümmerle-Deschner, J.B. Crupyrin-associated periodidic syndrome. Z. Rheumatol. 2012, 71, 199–208. [CrossRef] [PubMed]
182. Ahmadi, N.; Brewer, C.C.; Zalewski, C.; King, K.A.; Butman, J.A.; Plass, N.; Henderson, C.; Goldbach-Mansky, R.; Kim, H.J. Crupyrin-associated periodidic syndromes: Otologyngologic and audiologic manifestations. Otolaryngol. Head Neck Surg. Off. J. Am. Acad. Otolaryngol. Head Neck Surg. 2011, 145, 295–302. [CrossRef] [PubMed]
183. Kuemmerle-Deschner, J.B.; Ozen, S.; Tyrrell, P.N.; Kone-Paut, I.; Goldbach-Mansky, R.; Lachmann, H.; Blank, N.; Hoffman, H.M.; Weissbarth-Riedel, E.; Hugle, B.; et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). Ann. Rheum. Dis. 2017, 76, 942–947. [CrossRef] [PubMed]
184. Chen, P.; He, L.; Fang, X.; Wang, X.; Yang, T.; Wu, H. NLRP3 Is Expressed in the Spiral Ganglion Neurons and Associated with Both Syndromic and Nonsyndromic Sensorineural Deafness. Neural Plastic. 2015, 2015, bav071. [CrossRef]
185. Nakanishi, H.; Kawashima, Y.; Kurima, K.; Chae, J.J.; Ross, A.M.; Pinto-Patarroyo, G.; Patel, S.K.; Musket, J.A.; Ratay, J.S.; Chattaraj, P.; et al. NLRP3 mutation and coid ear inflammation cause syndromic and nonsyndromic hearing loss DFNA34 responsive to anakinra therapy. Proc. Natl. Acad. Sci. USA 2017, 114, E7766–E7775. [CrossRef]
186. Nakanishi, H.; Prakash, P.; Ito, T.; Kim, H.J.; Brewer, C.C.; Harrow, D.; Roux, I.; Hosokawa, S.; Griffith, A.J. Genetic Hearing Loss Associated with Autoinflammation. Front. Neurol. 2020, 11. [CrossRef]
187. Barisic, J.; Tokic, V.; Loane, M.; Bianchi, F.; Calzolari, E.; Garne, E.; Wellesley, D.; Dol, H. Descriptive epidemiology of Cornelia de Lange syndrome in Europe. Am. J. Med. Genet. 2008, 146a, 51–59. [CrossRef]
188. Borck, G.; Zarhrate, M.; Bonnefont, J.P.; Munnich, A.; Cormier-Daire, V.; Colleaux, L. Incidence and clinical features of X-linked Cornelia de Lange syndrome due to SMCL1 mutations. Hum. Mutat. 2007, 28, 205–206. [CrossRef]
189. Harris, C.M.; Shawkat, F.; Russell-Eggitt, I.; Wilson, J.; Taylor, D. Intermittent horizontal sacciade failure (‘ocular motor apraxia’) in children. Br. J. Ophthalmol. 1996, 80, 151–158. [CrossRef]
190. Tonkin, E.T.; Wang, T.J.; Liso, S.; Bamshad, M.J.; Strachan, T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and by Nipped-B, is mutated in Cornelia de Lange syndrome. Nat. Genet. 2004, 36, 636–641. [CrossRef]
191. Deardorff, M.A.; Bando, M.; Nakato, R.; Watrin, E.; Chae, J.J.; Ross, A.M.; Pinto-Patarroyo, G.; Patel, S.K.; Musket, J.A.; Ratay, J.S.; Chattaraj, P.; et al. NLRP3 mutation and coid ear inflammation cause syndromic and nonsyndromic hearing loss DFNA34 responsive to anakinra therapy. Proc. Natl. Acad. Sci. USA 2017, 114, E7766–E7775. [CrossRef]
192. Deardorff, M.A.; Porter, N.J.; Christianson, D.W. Structural, Functional, and Clinical Characterization of a Novel PTPN11 Mutation Cluster Underlying Noonan Syndrome. Mol. Genet. Genomic. 2006, 275, 1007–1027. [CrossRef] [PubMed]
193. Krantz, I.D.; McCallum, J.; DeScipio, C.; Kaur, M.; Gillis, L.A.; Yaeger, D.; Jukofsky, L.; Wasserman, N.; Bottani, A.; Morris, C.A.; et al. Structural, Functional, and Clinical Characterization of a Novel PTPN11 Mutation Cluster Underlying Noonan Syndrome. Mol. Genet. Genomic. 2006, 275, 1007–1027. [CrossRef] [PubMed]
194. Uhl, L.; Hungerford, K.; Borck, G.; Zarhrate, M.; Bonnefont, J.P.; Munnich, A.; Cormier-Daire, V.; Colleaux, L. Incidence and clinical features of X-linked Cornelia de Lange syndrome due to SMCL1 mutations. Hum. Mutat. 2007, 28, 205–206. [CrossRef]
195. Deardorff, M.A.; Porter, N.J.; Christianson, D.W. Structural aspects of HDAC8 mechanism and dysfunction in Cornelia de Lange syndrome spectrum disorders. Nat. Genet. 2004, 36, 631–635. [CrossRef] [PubMed]
196. Deardorff, M.A.; Kaur, M.; Yaeger, D.; Rampuria, A.; Korolev, S.; Pie, J.; Gil-Rodriguez, C.; Arnedo, M.; Loey, B.; Kline, A.D.; et al. Mutations in cDNA complex member SMC3 and SMC1A cause a mild variant of cornelia de Lange syndrome with predominant mental retardation. Am. J. Hum. Genet. 2007, 80, 485–494. [CrossRef] [PubMed]
197. Deardorff, M.A.; Wilde, J.J.; Albrecht, M.; Dickinson, E.; Tennstedt, S.; Braunholz, D.; Monnich, M.; Yan, Y.; Xu, W.; Gil-Rodriguez, M.C.; et al. RAD21 mutations cause a human cohesinopathy. Am. J. Hum. Genet. 2012, 90, 1014–1027. [CrossRef] [PubMed]
198. Krantz, I.D.; McCallum, J.; DeScipio, C.; Kaur, M.; Gillis, L.A.; Yaeger, D.; Jukošy, L.; Wasserman, N.; Bottani, A.; Morris, C.A.; et al. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. Nat. Genet. 2004, 36, 631–635. [CrossRef] [PubMed]
199. Deardorff, M.A.; Porter, N.J.; Christianson, D.W. Structural aspects of HDAC8 mechanism and dysfunction in Cornelia de Lange syndrome spectrum disorders. Nat. Genet. 2004, 36, 631–635. [CrossRef] [PubMed]
200. Murisier, F.; Guichard, S.; Beermann, F. The tyrosinase enhancer is activated by Sox10 and Mitf in mouse melanocytes. Pigment. Cell Res. 2007, 20, 173–184. [CrossRef] [PubMed]
201. Zhang, H.; Luo, H.; Chen, H.; Mei, L.; He, C.; Jiang, L.; Li, J.-D.; Feng, Y. Functional analysis of MITF gene mutations associated with Waardenburg syndrome type 2. FEBS Lett. 2012, 586, 4126–4131. [CrossRef] [PubMed]
202. Lee, H.-O.; Levorse, J.M.; Shin, M.K. The endothelin receptor-B is required for the migration of neural crest-derived melanocyte and enteric neuron precursors. Dev. Biol. 2003, 259, 162–175. [CrossRef]
203. Ichihashi, M.; Fujiwara, Y.; Uehara, Y.; Matsumoto, A. A mild form of xeroderma pigmentosum assigned to complementation group G and its repair heterogeneity. J. Investig. Dermatol. 1985, 85, 284–287. [CrossRef]
204. Pannone, L.; Bocchinfuso, G.; Flex, E.; Rossi, C.; Baldassarre, G.; Lissewski, C.; Pantaleoni, F.; Consoli, F.; Lepri; F.; Magliozzi, M.; et al. Structural, Functional, and Clinical Characterization of a Novel PTPN11 Mutation Cluster Underlying Noonan Syndrome. Hum. Mutat. 2017, 38, 451–459. [CrossRef] [PubMed]
207. Brennan, D.F.; Dar, A.C.; Hertz, N.T.; Chao, W.C.; Burlingame, A.L.; Shokat, K.M.; Barford, D. A Raf-induced allosteric transition of KSR stimulates phosphorylation of MEK. *Nature* **2011**, *472*, 366–369. [CrossRef]

208. Lavoie, H.; Sahmi, M.; Maisonneuve, F.; Marullo, S.A.; Thevakan, N.; Jin, T.; Kurinov, I.; Sicheri, F.; Therrien, M. MEK drives BRAF activation through allosteric control of KSR proteins. *Nature* **2018**, *554*, 549–553. [CrossRef]

209. Stephens, R.M.; Sthananandam, G.; Copeland, T.D.; Kaplan, D.R.; Rapp, U.R.; Morrison, D.K. 95-kilodalton B-Raf serine/threonine kinase: Identification of the protein and its major autophosphorylation site. *Mol. Cell. Biol.* **1992**, *12*, 3733–3742. [CrossRef]

210. Motegi, S.I.; Yokoyama, Y.; Ogino, S.; Yamada, K.; Uchiyama, A.; Takeuchi, Y.; Ohnishi, H.; Ishikawa, O. New insights into the pathogenesis of multiple lentigines in LEOPARD syndrome with PTEN1 gene mutation. *J. Dermatol. Sci.* **2016**, 84, e142. [CrossRef]

211. Chang, Y.-S.; Ahn, J.; Hong, S.H.; Kim, E.; Chung, W.-H.; Cho, Y.-S.; Moon, I.J. Case Series Outcomes of Cochlear Implantation in Children with Noonan Syndrome. *Korean J. Otorhinolaryngol. -Head Neck Surg.* **2019**, *62*. [CrossRef]

212. Mortiwaki, S.; Kanda, F.; Hayashi, M.; Yamashita, D.; Sakai, Y.; Nishigori, C.; Xeroderma pigmentosum Clinical Practice Guidelines Revision Committee. Xeroderma pigmentosum clinical practice guidelines. *J. Dermatol. Sci.* **2017**, *44*, 897–904. [CrossRef]

213. Beltramello, M.; Piazza, V.; Bukauskas, F.F.; Pozzan, T.; Mammano, F. Impaired permeability to Ins(1,4,5)P3 in a mutant connexin. *Carcinogenesis* **1997**, *18*, 897–904. [CrossRef]

214. Viana, L.M.; Seyyedi, M.; Brewer, C.C.; Zalewski, C.; DiGiovanna, J.J.; Tamura, D.; Totonchy, M.; Kraemer, K.H.; Nadol, J.B., Jr. Histopathology of the inner ear in patients with xeroderma pigmentosum and neurologic degeneration. *Korean J. Otorhinolaryngol. -Head Neck Surg.* **2019**, *62*, 1087–1096. [CrossRef]

215. Wang, C.M.; Lincoln, J.; Cook, J.E.; Becker, D.L. Abnormal connexin expression underlies delayed wound healing in diabetic skin. *Diabetes* **2007**, *56*, 2809–2817. [CrossRef]

216. Andera, L.; Wasylyk, B. Transcription Abnormalities Potentiate Apoptosis of Normal Human Fibroblasts. *Carcinogenesis* **1997**, *18*, 633–644. [CrossRef]

217. Dumaz, N.; van Kranen, H.J.; de Vries, A.; Berg, R.J.; Wester, P.W.; van Kreijl, C.F.; Sarasin, A.; Daya-Grosjean, L.; de Gruijl, F.R. The role of UV-B light in skin carcinogenesis through the analysis of p53 mutations in squamous cell carcinomas of hairless mice. *Oncogene* **2005**, *24*, 6567–6576. [CrossRef]

218. Rosania, G.R. Mitochondria Give Cells a Tan. *Carcinogenesis* **1997**, *897–904*. [CrossRef]

219. McKay, B.C.; Becerril, C.; Ljungman, M. P53 plays a protective role against UV- and cisplatin-induced apoptosis in transcription-coupled repair proficient fibroblasts. *Oncogene* **2001**, *20*, 6805–6808. [CrossRef]

220. Wilson, B.T.; Stark, Z.; Sutton, R.E.; Danda, S.; Ebkote, A.V.; Elsayed, S.M.; Gibson, L.; Goddish, J.A.; Jackson, A.P.; Keng, W.T.; et al. The Cockayne Syndrome Natural History (CoSyNH) study: Clinical findings in 102 individuals and recommendations for care. *Genet. Med.* **2016**, *18*, 483–493. [CrossRef]

221. Viana, L.M.; Seyyedi, M.; Brewer, C.C.; Zalewski, C.; DiGiovanna, J.J.; Tamura, D.; Totonchy, M.; Kraemer, K.H.; Nadol, J.B., Jr. Histopathology of the inner ear in patients with xeroderma pigmentosum and neurologic degeneration. *Otol. Neurotol.* **2013**, *34*, 1230–1239. [CrossRef]

222. Hervé, J.C.; Derangeon, M. Gap-junction-mediated cell-to-cell communication. *Cell Tissue Res.* **2013**, *352*, 252–31. [CrossRef] [PubMed]

223. Del Castillo, F.J.; Rodríguez-Ballesteros, M.; Alvarez, A.; Hutchin, T.; Leonardi, E.; de Oliveira, C.A.; Azaiiez, H.; Brownstein, Z.; Avenarius, M.R.; Marlin, S.; et al. A novel deletion involving the connexin-30 gene, del(GJB6-d13s1854), found in trans with XG mutation underlies recessive hereditary deafness. *Nat. Genet.* **2005**, *37*, 633–644. [CrossRef]

224. Avenarius, M.R.; Marlin, S.; et al. A novel deletion involving the connexin-30 gene, del(GJB6-d13s1854), found in trans with XG mutation underlies recessive hereditary deafness. *Nat. Genet.* **2005**, *37*, 633–644. [CrossRef]

225. Coutinho, P.; Qiu, C.; Frank, S.; Tamber, K.; Becker, D. Dynamic changes in connexin expression correlate with key events in the wound healing process. *Cell Biol. Int.* **2003**, *27*, 525–541. [CrossRef]

226. Lucke, T.; Choudhry, R.; Thom, R.; Selmer, I.S.; Burden, A.D.; Hodgins, M.B. Upregulation of connexin 26 is a feature of keratinocyte differentiation in hyperproliferative epidermids, vaginal epithelium, and buccal epithelium. *J. Investig. Dermatol.* **1999**, *112*, 354–361. [CrossRef]

227. Rouan, F.; White, T.W.; Brown, N.; Taylor, A.M.; Lucke, T.W.; Paul, D.L.; Munro, C.S.; Uitto, J.; Hodgins, M.B.; Richard, G. trans-dominant inhibition of connexin-43 by mutant connexin-26: Implications for dominant connexin disorders affecting epidermal differentiation. *J. Cell Sci.* **2001**, *114*, 2105–2113. [CrossRef]

228. Lilly, E.; Sellitto, C.; Milstone, L.M.; White, T.W. Connexin channels in congenital skin disorders. *Semin. Cell Dev. Biol.* **2016**, *50*, 4–12. [CrossRef]

229. Wang, C.M.; Lincoln, J.; Cook, J.E.; Becker, D.L. Abnormal connexin expression underlies delayed wound healing in diabetic skin. *Diabetes* **2007**, *56*, 2809–2817. [CrossRef]

230. Beltramello, M.; Piazza, V.; Bukauskas, F.F.; Pozzan, T.; Mammano, F. Impaired permeability to Ins(1,4,5)P3 in a mutant connexin underlies recessive hereditary deafness. *Nat. Cell Biol.* **2005**, *7*, 63–69. [CrossRef]

231. Jagger, D.J.; Forge, A. Connexins and gap junctions in the inner ear—it’s not just about K+ recycling. *Cell Tissue Res.* **2015**, *360*, 633–644. [CrossRef] [PubMed]
232. Cohen-Salmon, M.; Regnault, B.; Cayet, N.; Caille, D.; Demuth, K.; Hardelin, J.P.; Janel, N.; Meda, P.; Petit, C. Connexin30 deficiency causes intrastrial fluid-blood barrier disruption within the cochlear stria vascularis. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6229–6234. [CrossRef] [PubMed]

233. Common, J.E.; O’Toole, E.A.; Leigh, I.M.; Thomas, A.; Griffiths, W.A.; Venning, V.; Grabcysnas, S.; Peris, Z.; Kansky, A.; Kelsell, D.P. Clinical and genetic heterogeneity of erythrokeratoderma variabilis. *J. Investig. Dermatol.* **2005**, *125*, 920–927. [CrossRef] [PubMed]

234. Chouk, C.; Litalien, N. Erythrokeratoderma Variabilis. In *StatPearls*; StatPearls Publishing LLC.: Treasure Island, FL, USA, 2020.

235. Li, T.C.; Wang, W.H.; Li, C.; Yang, J.J. Association between mutations in the gap junction β4 gene and nonsyndromic hearing loss: Genotype-phenotype correlation patterns. * Mol. Mol. Rep.* **2015**, *11*, 619–624. [CrossRef] [PubMed]

236. Yang, J.J.; Wang, W.H.; Lin, Y.C.; Wang, H.H.; Yang, J.T.; Hwang, C.F.; Wu, C.M.; Li, S.Y. Prospective variants screening of connexin genes in children with hearing impairment: Genotype/phenotype correlation. *Human Genet.* **2010**, *128*, 303–313. [CrossRef] [PubMed]

237. Kooshavar, D.; Tabatabaiefar, M.A.; Farrokhi, E.; Abolhasani, M.; Noori-Daloii, M.R.; Hashemzadeh-Chaleshtori, M. Digenic inheritance in autosomal recessive non-syndromic hearing loss cases carrying GJB2 heterozygote mutations: Assessment of GJB4, GJA1, and GJC3. *Int. J. Pediatric Otorhinolaryngol.* **2013**, *77*, 189–193. [CrossRef]

238. Laleh, M.A.; Naseri, M.; Zonouzi, A.A.P.; Zonouzi, A.P.; Masoudi, M.; Ahangari, N.; Shams, L.; Nejatizadeh, A. Diverse pattern of gap junction β-2 and gap junction β-4 genes mutations and lack of contribution of DFNB21, DFNB24, DFNB29, and DFNB42 loci in autosomal recessive nonsyndromic hearing loss patients in Hormozgan, Iran. *J. Res. Med. Sci.* **2017**, *22*, 99. [CrossRef]

239. Church, V.L.; Francis-West, P. Wnt signalling during limb development. *Int. J. Dev. Biol.* **2002**, *46*, 927–936.

240. Dobrowolski, R.; Vick, P.; Ploter, D.; Gummer, I.; Snitkin, H.; Sabatini, D.D.; De Robertis, E.M. Presenilin deficiency or lysosomal deficiency of locomotion in neural crest cell migration. *Cell Rep.* **2012**, *2*, 1316–1328. [CrossRef]

241. Geetha-Loganathan, P.; Nimmagadda, S.; Scaal, M. Wnt signaling in limb organogenesis. *Organogenesis* **2008**, *4*, 109–115. [CrossRef]

242. Corbett, M.A.; Sahlo, M.; Jolly, L.; Afawi, Z.; Gardner, A.E.; Oliver, K.L.; Tan, S.; Coffey, A.; Mulley, J.C.; Dibbens, L.M.; et al. A focal epilepsy and intellectual disability syndrome is due to a mutation in TBC1D24. *Am. J. Hum. Genet.* **2010**, *87*, 371–375. [CrossRef] [PubMed]

243. Palace, A.; Filippello, F.; La Padula, V.; Vanni, N.; Mafia, F.; De Pietri Tonelli, D.; de Falco, F.A.; Striano, P.; Dagna Bricarelli, F.; Minetti, C.; et al. TBC1D24, an ARF6-interacting protein, is mutated in familial infantile myoclonic epilepsy. *Am. J. Hum. Genet.* **2010**, *87*, 365–370. [CrossRef] [PubMed]

244. Yoon, J.; Hwang, Y.-S.; Lee, M.; Sun, J.; Cho, H.J.; Knapik, L.; Daar, I.O. TBC1d24-ephrinB2 interaction regulates contact inhibition of locomotion in neural crest cell migration. *Nat. Commun.* **2018**, *9*, 3491. [CrossRef] [PubMed]

245. Azaiez, H.; Booth, K.T.; Bu, F.; Huygen, P.; Shibata, S.B.; Shearer, A.E.; Kolbe, D.; Meyer, N.; Black-Ziegelbein, E.A.; Smith, R.J. Restoration of β gap junction gene and nonsyndromic hearing loss: Genotype-phenotype correlation. *Mol. Genet. Metab.* **2014**, *112*, 819–823. [CrossRef] [PubMed]

246. Imamura, A.; Shimozawa, N.; Suzuki, Y.; Zhang, Z.; Tsukamoto, T.; Fujiki, Y.; Orii, T.; Osumi, T.; Kondo, N. Restoration of biochemical function of the peroxisome in the temperature-sensitive mild forms of peroxisome biogenesis disorder in humans. *Brain Dev.* **2000**, *22*, 8–12. [CrossRef]

247. Mardones, P.; Hetz, C. Peroxisomes Get Loud: A Redox Antidote to Hearing Loss. *Cell 2015*, **163**, 790–791. [CrossRef]

248. Wang, A.C.; Ryan, A.F. Mechanisms of sensorineural cell damage, death and survival in the cochlea. *Clin. Exp. Pharmacol. Physiol.* **2008**, *35*, 119–123. [CrossRef] [PubMed]

249. Nichols, D.H.; Pauley, S.; Jahan, I.; Beisel, K.W.; Millen, K.J.; Fritzsch, B. Lmx1a is required for segregation of sensory epithelia and normal ear histogenesis and morphogenesis. *Cell Tissue Res.* **2008**, *334*, 339–358. [CrossRef]

250. Cowin, A.J.; Adams, D.; Geary, S.M.; Wright, M.D.; Jones, J.C.; Ashman, L.K. Wound healing is defective in mice lacking tetraspanin CD151. *J. Investig. Dermatol. 2006*, *126*, 680–689. [CrossRef]

251. Liu, W.; Atturo, F.; Aldaya, R.; Santì, P.; Cureoglu, S.; Obwegeser, S.; Glueckert, R.; Pfaller, K.; Schott-Fischer, A.; Rask-Andersen, H. Macromolecular organization and fine structure of the human basilar membrane—RELEVANCE for cochlear implantation. *Cell Tissue Res.* **2015**, *360*, 245–262. [CrossRef]

252. Pillers, D.-A.M.; Kempton, J.B.; Duncan, N.M.; Pang, J.; Dvinnell, S.J.; Trune, D.R. Hearing loss in the laminin-deficient dy mouse model of congenital muscular dystrophy. *Mol. Genet. Metab. 2002*, *76*, 217–224. [CrossRef]

253. Rohrbach, M.; Spencer, H.L.; Porter, L.F.; Burkitt-Wright, E.M.; Bürer, C.; Janecke, A.; Bakshi, M.; Sillence, D.; Al-Hussain, H.; Baumgartner, M.; et al. ZNF469 frequently mutated in the brittle cornea syndrome (BCS) is a single exon gene possibly regulating expression of several extracellular matrix components. *Mol. Genet. Metab. 2013*, *109*, 289–295. [CrossRef] [PubMed]

254. Galli, G.G.; Honnens de Lichtenberg, K.; Carrara, M.; Hans, W.; Welling, M.; Mentz, B.; Multhaupt, H.A.; Fog, C.K.; Jensen, K.T.; Rapppsibler, J.; et al. Prdm5 regulates collagen gene transcription by association with RNA polymerase II in developing bone. *PloS Genet.* **2012**, *8*, e1002711. [CrossRef] [PubMed]

255. Mizumoto, S.; Kosho, T.; Yamada, S.; Sugahara, K. Pathophysiological Significance of Dermatan Sulfate Proteoglycans Revealed by Human Genetic Disorders. *Pharmaceuticals* **2017**, *10*, 34. [CrossRef]
256. Müller, T.; Mizumoto, S.; Suresh, I.; Komatsu, Y.; Vodopiutz, J.; Dundar, M.; Straub, V.; Lingenhel, A.; Melmer, A.; Lechner, S.; et al. Loss of dermatan sulfate epimerase (DSE) function results in musculocontractural Ehlers-Danlos syndrome. *Hum. Mol. Genet.* 2013, 22, 3761–3772. [CrossRef]

257. Slepecky, N.B.; Henderson, C.G.; Saha, S. Post-translational modifications of tubulin suggest that dynamic microtubules are present in sensory cells and stable microtubules are present in supporting cells of the mammalian cochlea. *Hear. Res.* 1995, 91, 136–147. [CrossRef]

258. Cai, Q.; Du, X.; Zhou, B.; Cai, C.; Kermany, M.H.; Yoo, T. Induction of tolerance by oral administration of $\beta$-tubulin in an animal model of autoimmune inner ear disease. *ORL J. Otorhinolaryngol. Relat. Spec.* 2009, 71, 135–141. [CrossRef]

259. Du, X.; Yoo, T.; Mora, R. Distribution of $\beta$-tubulin in guinea pig inner ear. *ORL J. Otorhinolaryngol. Relat. Spec.* 2003, 65, 7–16. [CrossRef]

260. Riente, L.; Bongiorni, F.; Nacci, A.; Migliorini, P.; Segnini, G.; Delle Sedie, A.; Ursino, F.; Tommasi, S.; Fattori, B. Antibodies to inner ear antigens in Meniere's disease. *Clin. Exp. Immunol.* 2004, 135, 159–163. [CrossRef]

261. Yoo, T.J.; Du, X.; Kwon, S.S. Molecular mechanism of autoimmune hearing loss. *Acta Otolaryngol. Suppl.* 2002, 122, 3–9. [CrossRef]

262. Yoo, T.J.; Shea, J., Jr.; Ge, X.; Kwon, S.S.; Yazawa, Y.; Sener, O.; Mora, F.; Mora, R.; Mora, M.; Barbieri, M.; et al. Presence of autoantibodies in the sera of Meniere's disease. *Ann. Otol. Rhinol. Laryngol.* 2001, 110, 425–429. [CrossRef] [PubMed]

263. Zhou, B.; Kermany, M.H.; Cai, Q.; Cai, C.; Zhou, Y.; Nair, U.; Liu, W.; Yoo, T.J. Experimental autoimmune hearing loss is exacerbated in IL-10-deficient mice and reversed by IL-10 gene transfer. *Gene Ther.* 2012, 19, 228–235. [CrossRef] [PubMed]

264. Zhou, B.; Kermany, M.H.; Glickstein, J.; Cai, Q.; Cai, C.; Zhou, Y.; Nair, U.; Kim, J.W.; Kim, P.; Liu, W.; et al. Murine autoimmune hearing loss mediated by CD4+ T cells specific for $\beta$-tubulin. *Clin. Immunol.* 2011, 138, 222–230. [CrossRef] [PubMed]

265. Yoo, T.J.; Tanaka, H.; Kwon, S.S.; Mora, F.; Mora, R.; Yazawa, Y.; Suzuki, M.; Kitajima, K. $\beta$-Tubulin as an autoantigen for autoimmune inner ear disease. *Int. Congr. Ser.* 2003, 1240, 1207–1210. [CrossRef]

266. Elmore, S. Apoptosis: A review of programmed cell death. *Toxicol Pathol* 2007, 35, 495–516. [CrossRef]

267. Scheffel, J.; Mahnke, N.A.; Hofman, Z.L.M.; Maat, S.D.; Wu, J.; Bonnekoh, H.; Pengelly, R.J.; Ennis, S.; Holloway, J.W.; Kirchner, M.; et al. Cold-induced urticarial autoinflammatory syndrome related to factor XII activation. *Nat. Commun.* 2020, 11, 179. [CrossRef]

268. Vambutas, A.; Lesser, M.; Mullol, V.; Pathak, S.; Zahtz, G.; Rosen, L.; Goldofsky, E. Early efficacy trial of anakinra in corticosteroid-resistant autoimmune inner ear disease. *J. Clin. Investig.* 2014, 124, 4115–4122. [CrossRef]

269. Nakamura, Y.; Kambe, N.; Saito, M.; Nishikomori, R.; Nishikomiri, R.; Kim, Y.-G.; Murakami, M.; Nunez, G.; Matsue, H. Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria. *J. Exp. Med.* 2009, 206, 1037–1046. [CrossRef]

270. Hirose, K.; Discolo, C.M.; Keasler, J.R.; Ransohoff, R. Mononuclear phagocytes migrate into the murine cochlea after acoustic trauma. *J. Comp. Neurol.* 2005, 489, 180–194. [CrossRef]

271. Mariathasan, S.; Weiss, D.S.; Newton, K.; McBride, J.; O’Rourke, K.; Roose-Girma, M.; Lee, W.P.; Weinrauch, Y.; Monack, D.M.; Dixit, V.M. Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* 2006, 440, 228–232. [CrossRef]

272. Sutterwala, F.S.; Ogura, Y.; Szczepanik, M.; Lara-Tejero, M.; Lichtenberger, G.S.; Grant, E.P.; Bertin, J.; Coyle, A.J.; Galán, J.E.; Askenase, P.W.; et al. Critical role for NALP3/CIRS1/Cryopyrin in innate and adaptive immunity through its regulation of caspase-1. *Immunity* 2006, 24, 317–327. [CrossRef] [PubMed]