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Hidrotic Ectodermal Dysplasia 2

Synonym: Clouston Syndrome

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Summary

Clinical characteristics

Hidrotic ectodermal dysplasia 2, or Clouston syndrome (referred to as HED2 throughout this *GeneReview*) is characterized by a triad of major clinical features including partial-to-complete alopecia, nail dystrophy, and palmoplantar hyperkeratosis. Sweating is preserved and there are usually no dental anomalies.

Sparse scalp hair and dysplastic nails are seen early in life. In infancy, scalp hair is fine, sparse, and brittle. Progressive hair loss may lead to total alopecia by puberty. The nails may be milky white in early childhood; they gradually become dystrophic, thick, and distally separated from the nail bed. Palmoplantar keratoderma may develop during childhood and increases in severity with age. Associated features may include cutaneous hyperpigmentation (particularly over the joints) and finger clubbing. The clinical manifestations are highly variable even within the same family.

Diagnosis/testing

The diagnosis of HED2 is established in a proband with suggestive findings and a heterozygous pathogenic variant in *GJB6* identified by molecular genetic testing. Targeted analysis for the four most common *GJB6* pathogenic variants detects pathogenic variants in approximately 100% of affected individuals.

Management

Treatment of manifestations: Special hair care products to help manage dry and sparse hair; wigs; artificial nails; emollients and keratolytics to relieve palmoplantar hyperkeratosis.

Genetic counseling

HED2 is inherited in an autosomal dominant manner. Most individuals with HED2 have an affected parent; *de novo* pathogenic variants have also been reported. Offspring of affected individuals have a 50% chance of inheriting the pathogenic variant and being affected. Once the causative *GJB6* pathogenic variant has been

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identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for HED2 are possible.

Diagnosis

Suggestive Findings

Hidrotic ectodermal dysplasia 2 (HED2, Clouston syndrome) **should be considered** after infancy in individuals with the following clinical features:

- **Nail dystrophy** (malformed, thickened, small nails); an essential feature of the syndrome. In approximately 30% of affected persons, nail dystrophy may be the only obvious finding during the physical examination at a specific time.
- **Hypotrichosis** (partial or total alopecia). The scalp hair is sparse, pale, fine, and brittle, or may be completely absent. The eyebrows are sparse or absent. The eyelashes are short and sparse. Axillary and pubic hair is sparse or absent.
- **Palmoplantar hyperkeratosis** (hyperkeratosis of the palms and soles); a common but not universal finding

Establishing the Diagnosis

The molecular diagnosis of HED2 **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GJB6* identified by molecular genetic testing (see Table 1).

Note: Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *GJB6* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with ectodermal dysplasia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing

- **Targeted analysis** for the four known *GJB6* pathogenic variants p.Gly11Arg, p.Ala88Val, p.Val37Glu, p.Asp50Asn can be performed first.
- **Sequence analysis** of *GJB6* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. Note: To date such variants have not been identified as a cause of this disorder.

A multigene panel that includes *GJB6* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition in a cost-effective manner while limiting detection of variants of uncertain significance and unrelated pathogenic variants. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by ectodermal dysplasia, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of this disorder.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hidrotic Ectodermal Dysplasia 2

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GJB6	Targeted analysis for pathogenic variants [3]	100% [4]
	Sequence analysis [5]	100% [4]
	Deletion/duplication analysis [6]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Pathogenic variants detected include p.Gly11Arg, p.Ala88Val, p.Val37Glu, and p.Asp50Asn. See Molecular Genetics for populations with these pathogenic variants. Note: Pathogenic variants included in a panel may vary by laboratory.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020].
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Hidrotic ectodermal dysplasia 2 (HED2, Clouston syndrome) is characterized by dystrophy of the nails, alopecia (partial or total), hyperpigmentation of the skin (especially over the joints), palmoplantar hyperkeratosis, and

clubbing of the fingers. Sweat glands, sebaceous glands, and teeth are normal. The clinical manifestations are highly variable even within the same family.

To date, more than 150 individuals with HED2 have been identified [Lamartine et al 2000a, Lamartine et al 2000b, Smith et al 2002, van Steensel et al 2003, Zhang et al 2003, Baris et al 2008, Chen et al 2010, Marakhonov et al 2012, Fujimoto et al 2013, Mousumi et al 2013, Sugiura et al 2013, Hu et al 2015, Agarwal et al 2016, Odell et al 2016, Pietrzak et al 2016, Yang et al 2016, Cammarata-Scalisi et al 2019, Khatter et al 2019, Shi et al 2019, Sukakul et al 2019, Zhan et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Hidrotic Ectodermal Dysplasia 2: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Sparse hair / Alopecia	100%	• Hair often sparse & fine w/progressive thinning & alopecia in adulthood • Involvement of eyebrows, lashes, & axillary & pubic hair
Dystrophic nails	100%	• Typically present from birth or early childhood; often short, thick & slow growing • May be cone shaped or triangular; may be assoc w/finger clubbing
Palmoplantar keratoderma	70%	• Onset usually from early childhood to adolescence; when present, may be focal or diffuse • Often has a cobblestoned appearance w/multiple small fissures • Hyperkeratosis may also be found on knuckles, knees, & elbows.

Hair. In infancy, the scalp hair is fine, wiry, brittle, patchy, and pale. Progressive hair loss may lead to total alopecia, usually by puberty, although alopecia totalis in infancy has also been reported. Eyebrows, eyelashes, and pubic and axillary hair are also typically sparse or absent.

Nails. In early childhood, the nails may be milky white. They gradually become dystrophic, thick, short, and distally separated from the nail bed. There may be vertical ridging (onychorrhexis), triangular nail plates, or absent nails. Nail growth is slow.

Skin. Palmoplantar keratoderma, which is absent in some pedigrees, increases in severity with age; when present, onset is from early childhood to adolescence. Changes are usually diffuse with or without a cobblestone appearance; in some individuals the keratoderma is more focal. There may be associated skin thickening and hyperpigmentation on the knuckles, knees, and elbows.

Teeth and ability to sweat are normal, as are physical growth and psychomotor development.

Genotype-Phenotype Correlations

Whereas most *GJB6* pathogenic variants cause the clinical presentations typical of HED2 (i.e., with involvement of the hair, nails, and palmoplantar skin), the p.Gly11Arg and p.Ala88Val pathogenic variants can be associated with a clinical picture similar to that of pachyonychia congenita [van Steensel et al 2003] (see Differential Diagnosis).

In some families, HED2 caused by the p.Gly11Arg pathogenic variant involved only hair and nails [Chen et al 2010, Hu et al 2015, Khatter et al 2019].

Penetrance

Penetrance is high [Hayflick et al 1996] – likely 100% [Author, personal observation].

Nomenclature

When referring to HED2 (Clouston syndrome), the nonspecific term "hidrotic ectodermal dysplasia" should not be used, as other forms of ectodermal dysplasia are associated with normal sweating.

Prevalence

HED2 is relatively common in the French-Canadian population of southwest Quebec [Kibar et al 2000]. The condition has also been reported in the US, particularly in Vermont, upstate New York, and Louisiana among communities of French-Canadian ancestry as well as among populations of African, Chinese, French, Indian, Thai, Irish, Malaysian, Scottish, Spanish, and Ashkenazi Jewish ancestry [Radhakrishna et al 1997, Taylor et al 1998, Kibar et al 2000, Zhang et al 2003, Baris et al 2008].

Genetically Related (Allelic) Disorders

Autosomal recessive nonsyndromic hearing loss (AR NSHL). About 1% of individuals with *GJB2*-related AR NSHL are compound heterozygotes for one *GJB2* pathogenic variant and one of several different deletions that include sequences upstream of *GJB2* (comprising either *GJB6* and portions of *CRYL1* or just portions of *CRYL1*) that delete *cis*-regulatory regions of *GJB2*, thereby abolishing *GJB2* expression (see *GJB2*-Related Autosomal Recessive Nonsyndromic Hearing Loss).

Sporadic neoplasms (including eccrine syringofibroadenomas) occurring as single tumors in the absence of any other findings of HED2 frequently contain a somatic variant in *GJB6* that is **not** present in the germline. In these circumstances, predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Various types of hidrotic ectodermal dysplasia exist, and it is likely that new types will be described [Wright et al 2019].

Hidrotic ectodermal dysplasia 2 (HED2) must be differentiated from other ectodermal dysplasias that can affect nails and hair (see Table 4).

Table 4. Ectodermal Dysplasias in the Differential Diagnosis of Hidrotic Ectodermal Dysplasia 2

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment / Distinguishing Features
EDA *EDAR* *EDARADD* *WNT10A*	Hypohidrotic ectodermal dysplasia (HED) [1]	XL AR AD	• Hypotrichosis: thin, lightly pigmented, slow-growing scalp hair • Hypohidrosis: deficient sweating w/ episodes of hyperthermia • Hypodontia: few & abnormally formed teeth erupt, later than average	• Hypohidrosis & dental abnormalities are the major distinguishing features. • Eyelid papules may develop in *WNT10A*-HED.
GJB2	Keratitis-ichthyosis-deafness syndrome (OMIM 148210)	AD	• Sensorineural deafness • Photophobia, corneal ulceration & scarring • Progressive hyperkeratotic plaques & palmoplantar hyperkeratosis • Sparse hair & nail dystrophy: less pronounced than in HED2	Sensorineural deafness & ocular changes are the major differentiating features.
HOXC13	Ectodermal dysplasia 9, hair/nail type (OMIM 614931)	AR	• Generalized congenital atrichia • Nail dystrophy	Absent palmoplantar keratoderma

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment / Distinguishing Features
KRT6A *KRT6B* *KRT6C* *KRT16* *KRT17*	Pachyonychia congenita (PC)	AD	• Hypertrophic nail dystrophy w/ subungual hyperkeratosis • Painful focal palmoplantar keratoderma & blistering • Variably present: oral leukokeratosis, pilosebaceous cysts, palmoplantar hyperhidrosis, follicular keratoses on the trunk & extremities, natal teeth	• Absence of hypotrichosis or atrichia is the main distinguishing feature. • Palmoplantar keratoderma is focal in PC (vs diffuse in most cases of HED2).
KRT74	Ectodermal dysplasia 7, hair/nail type (OMIM 614929)	AR	• Generalized hypotrichosis or atrichia • Nail dystrophy	Absent palmoplantar keratoderma
KRT85	Ectodermal dysplasia 4, hair/nail type (OMIM 602032)	AR	• Sparse or absent scalp hair • Absent eyebrows, eyelashes, pubic & axillary hair • Nail dystrophy	Absent palmoplantar keratoderma

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. EDA pathogenic variants are associated with X-linked HED. *EDAR*, *EDARADD*, and *WNT10A* pathogenic variants are associated with autosomal dominant and autosomal recessive HED.

Disorder of unknown genetic cause. Ectodermal dysplasia 5, hair/nail type (OMIM 614927) is an autosomal recessive form of ED, followed in 13 individuals over six generations from a consanguineous Pakistani family [Rafiq et al 2005]. The clinical features include severely dystrophic nails and thin scalp hair, fine eyebrows and eyelashes, and thin body hair. The associated gene is unknown.

Isolated nail dystrophy can also be a finding of Darier disease (OMIM 124200) and acquired disorders such as lichen planus and psoriasis. Associated symptoms and history should allow easy differentiation.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hidrotic ectodermal dysplasia 2 (HED2, Clouston syndrome), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Hidrotic Ectodermal Dysplasia 2

System/Concern	Evaluation	Comment
Integument	By dermatologist	Clinical exam to determine extent of disease & functional & psychosocial impact on the affected person.
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of HED2 in order to facilitate medical & personal decision making

HED2 = hidrotic ectodermal dysplasia 2; MOI= mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Hidrotic Ectodermal Dysplasia 2

Manifestation/ Concern	Treatment	Considerations/Other
Dystrophic nails	• Filing or drilling of hyperkeratotic nails • Artificial nails	• May improve appearance of hands/feet & ↓ trauma from footwear. • May be especially helpful to girls & women.
Hypotrichosis	• Conditioning hair care products may help to manage dry & sparse hair. • Wigs or hair weaves for alopecia • Use of artificial hair fibers to improve appearance of hair • Use of eyebrow tattoos	• Alopecia improved w/combination of topical minoxidil & tretinoin in a person w/clinical features of HED2. [1] • Alopecia improved w/topical minoxidil in a child w/hypohidrotic ED. [2]
Palmoplantar hyperkeratosis	• Bland skin emollients may help soften hyperkeratosis. • Keratolytic preparations (containing e.g. urea, salicylic acid, lactic acid) may be helpful. • Regular filing or paring of hard skin can ↓ pain & improve function.	Analgesics may be required for painful plantar keratoderma.

1. A molecular diagnosis of HED2 was not confirmed. The authors also noted that the efficacy and safety of long-term treatment need to be explored further [Melkote et al 2009].
2. Lee et al [2013]

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Tretinoin and minoxidil should be avoided in pregnancy.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hidrotic ectodermal dysplasia 2 (HED2) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with HED2 have an affected parent and a family history of other affected individuals in the same or previous generations.
- A proband with HED2 may have the disorder as the result of a *de novo GJB6* pathogenic variant [Smith et al 2002, Baris et al 2008]. The exact proportion of individuals with HED2 resulting from a *de novo* pathogenic variant is unknown but presumed to be low.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., a proband who appears to be the only affected family member).
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism; although no instances of germline mosaicism have been reported, it remains a possibility. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with HED2 may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (physical examination and molecular genetic testing for the pathogenic variant identified in the proband) have demonstrated that neither parent has manifestations of the disorder or is heterozygous for the pathogenic variant.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the *GJB6* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *GJB6* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for HED2 because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with HED2 has a 50% chance of inheriting the *GJB6* pathogenic variant and being affected.

Other family members The risk to other family members depends on the status of the proband's parents: if a parent has the *GJB6* pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *GJB6* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for HED2 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Ectodermal Dysplasia Society**
  United Kingdom
  Phone: 01242 261332
  Email: info@edsociety.co.uk
  www.edsociety.co.uk
- **Medline Plus**
  Ectodermal dysplasia
- **National Foundation for Ectodermal Dysplasias (NFED)**
  Phone: 618-566-2020
  Email: info@nfed.org
  www.nfed.org
- **Ectodermal Dysplasias International Registry**
  Email: info@nfed.org
  Ectodermal Dysplasias International Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hidrotic Ectodermal Dysplasia 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GJB6	13q12.11	Gap junction beta-6 protein	Hereditary Hearing Loss Homepage (GJB6) CCHMC - Human Genetics Mutation Database (GJB6) The Connexin-deafness homepage (GJB6)	GJB6	GJB6

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hidrotic Ectodermal Dysplasia 2 (View All in OMIM)

129500	CLOUSTON SYNDROME
604418	GAP JUNCTION PROTEIN, BETA-6; GJB6

Molecular Pathogenesis

Gap junction beta-6 protein comprises 261 amino acids and four transmembrane domains, two extracellular domains, and three cytoplasmic domains including the amino- and carboxy-terminal regions. Gap junction beta-6 protein, with five other similar subunits, forms a gap junction channel, the connexon, which mediates the direct diffusion of ions and metabolites between the cytoplasm of adjacent cells. *GJB6* is expressed most abundantly in brain and skin.

Mechanism of disease causation. The presence of the mutated protein may lead to a defect in trafficking of other gap junction protein subunits, since their oligomerization is complete upon entry into the Golgi apparatus [Evans et al 1999, van Steensel 2004]. Several pathogenic variants in genes encoding related gap junction proteins result in mistrafficking of the protein [Common et al 2002]. The association of HED2 with four different pathogenic variants in *GJB6* supports this idea. In that case, the pathogenic variants of *GJB6* should interfere with its incorporation into the gap junction. To date, this hypothesis has not been experimentally validated [van Steensel 2004]. However, evidence was provided that *GJB6* could be a transcriptional target gene of p63, elucidating further the process of the development of the skin and the morphogenesis of its appendages [Fujimoto et al 2013].

Table 7. Notable *GJB6* Pathogenic Variants

Reference Sequences	DNA Nuclotide Change	Predicted Protein Change	Comment [References]
NM_006783.4 NP_006774.2	c.31G>A	p.Gly11Arg	Found in persons of French, French-Canadian, African, Spanish, Scottish-Irish, & Chinese ancestry [Lamartine et al 2000a, Zhang et al 2003, Chen et al 2010, Hu et al 2015, Pietrzak et al 2016, Khatter et al 2019]
	c.263C>T	p.Ala88Val	Found in persons of Indian, Malaysian, Chinese, Japanese, & Russian ancestry [Lamartine et al 2000a, Lamartine et al 2000b, van Steensel et al 2003, Marakhonov et al 2012, Sugiura et al 2013, Yang et al 2016, Zhan et al 2020]
	c.110T>A	p.Val37Glu	Found in a simplex case (i.e., a single affected person in a family) of Scottish ancestry [Smith et al 2002]
	c.148G>A	p.Asp50Asn	Affects the first extracellular loop of the connexin 30 molecule; identified in a person of Scottish background [Smith et al 2002]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Certain *GJB6* variants associated with HED2 have been identified in eccrine syringofibroadenomas, a rare benign neoplasm derived from acrosyringium cells of the eccrine sudoriferous glands [Andrade et al 2014]. Syringofibrocarcinoma has been reported in an individual with Clouston syndrome and represents malignant transformation of eccrine syringofibroadenomas. This tumor arose on the foot and was managed surgically. Screening skin examinations should therefore be considered for individuals with Clouston syndrome [Odell et al 2016].

Chapter Notes

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