



Hypohidrotic Ectodermal Dysplasia

Synonyms: Anhidrotic Ectodermal Dysplasia, Christ-Siemens-Touraine Syndrome

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Summary

Clinical characteristics

Hypohidrotic ectodermal dysplasia (HED) is characterized by hypotrichosis (sparseness of scalp and body hair), hypohidrosis (reduced ability to sweat), and hypodontia (congenital absence of teeth). The cardinal features of classic HED become obvious during childhood. The scalp hair is thin, lightly pigmented, and slow growing. Sweating, although present, is greatly deficient, leading to episodes of hyperthermia until the affected individual or family acquires experience with environmental modifications to control temperature. Only a few abnormally formed teeth erupt, at a later-than-average age. Physical growth and psychomotor development are otherwise within normal limits. Mild HED is characterized by mild manifestations of any or all the characteristic features.

Diagnosis/testing

Classic HED can be diagnosed after infancy based on physical features in most affected individuals. Identification of a hemizygous *EDA* pathogenic variant in an affected male or biallelic *EDAR*, *EDARADD*, or *WNT10A* pathogenic variants in an affected male or female confirms the diagnosis.

The diagnosis of mild HED is established in a female by identification of a heterozygous *EDA*, *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant. The diagnosis of mild HED is established in a male by identification of a heterozygous *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant.

Management

Treatment of manifestations: Wigs or special hair care formulas for sparse, dry hair may be useful. Access to an adequate water supply and a cool environment during hot weather. Skin care products for eczema and exposures that exacerbate dry skin. Early dental treatment; bonding of conical teeth; orthodontics as necessary; dental implants in the anterior portion of the mandibular arch in older children; replacement of dental prostheses as

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needed, often every 2.5 years; dental implants in adults; dietary counseling for individuals with chewing and swallowing difficulties; therapeutics to maintain oral lubrication and control caries; fluoride treatment to prevent caries. Nasal and aural concretions may be removed with suction devices or forceps as needed by an otolaryngologist. Prevention of nasal concretions through humidification of ambient air is helpful. Lubrication eye drops. Management of recurrent respiratory infections and asthma per primary care provider with referral to allergist and/or pulmonologist as needed.

Surveillance: Dental evaluation by age one year with follow-up dental evaluations every six to 12 months. Assess for skin, hair, ophthalmologic, and respiratory manifestations annually and/or as needed. Assess for abnormal nasal and aural secretions annually and/or as needed.

Agents/circumstances to avoid: Exposure to extreme heat.

Evaluation of relatives at risk: If the family-specific pathogenic variant(s) are known, molecular genetic testing of at-risk relatives should be offered to permit early diagnosis and treatment, especially to avoid hyperthermia.

Pregnancy management: Optimal prenatal nutrition for mothers who are unaffected heterozygotes or those who are affected with HED. Affected women at risk for hyperthermia should not become overheated during pregnancy.

Genetic counseling

EDA-related HED is inherited in an X-linked manner. *EDAR*-, *EDARADD*-, and *WNT10A*-related HED are inherited in an autosomal recessive or an autosomal dominant manner.

- **X-linked HED.** If the mother of a proband is heterozygous for an *EDA* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. If the father of the proband has an *EDA* pathogenic variant, he will transmit it to all his daughters and none of his sons. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may show manifestations of ectodermal dysplasia. Molecular genetic identification of female heterozygotes requires prior identification of the *EDA* pathogenic variant in the family.
- **Autosomal recessive HED.** The parents of a child with autosomal recessive HED are presumed to be heterozygous for a pathogenic variant in *EDAR*, *EDARADD*, or *WNT10A*. If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Heterozygote detection for at-risk relatives requires prior identification of the *EDAR*, *EDARADD*, or *WNT10A* pathogenic variants in the family.
- **Autosomal dominant HED.** Some individuals diagnosed with autosomal dominant HED have an affected parent. Each child of an individual with autosomal dominant HED has a 50% chance of inheriting the *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant.

Once the *EDA*, *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for HED are possible.

GeneReview Scope

Hypohidrotic Ectodermal Dysplasia: Included Phenotypes

- Classic hypohidrotic ectodermal dysplasia
- Mild hypohidrotic ectodermal dysplasia

For synonyms and outdated names see Nomenclature.

Diagnosis

No guidelines regarding diagnostic criteria for hypohidrotic ectodermal dysplasia (HED) have been developed.

Suggestive Findings

HED **should be suspected** in an individual with:

- **Hypotrichosis** (sparseness of scalp and body hair). Scalp hair has thin shafts and is lightly pigmented. Note: Hair shafts can be brittle and twisted (*pili torti*) or have other anomalies on microscopic analysis; however, these findings are not sufficiently sensitive to be of diagnostic benefit [Rouse et al 2004]. Secondary sexual hair (beard; axillary and pubic hair) can be normal.
- **Hypohidrosis** (reduced ability to sweat). Reduced ability to sweat in response to heat leads to hyperthermia:
 - The function of sweat glands may be assessed by bringing the skin into contact with an iodine solution and raising ambient temperatures to induce sweating. The iodine solution turns color when exposed to sweat and can be used to determine the amount and location of sweating.
 - The number and distribution of sweat pores can be determined by coating parts of the body (usually the hypothenar eminences of the palms) with impression materials commonly used by dentists.
 - While skin biopsies have been used to determine the distribution and morphology of sweat glands, noninvasive techniques are equally effective. Live confocal microscope imaging is able to visualize the sweat ducts on the palms [Jones et al 2013].
- **Hypodontia** (congenital absence of teeth):
 - An average of nine permanent teeth, frequently the canines and first permanent molars, develop in individuals with classic HED, but tooth number and distribution are highly variable [Lexner et al 2007].
 - Teeth are often smaller than average and have an altered morphology; the anterior teeth frequently have conical crowns.
 - Dental radiographs are helpful for determining the extent of hypodontia and are useful in the diagnosis of mildly affected individuals. Taurodontism (elongation of the pulp chamber) is more common in molar teeth of individuals with HED than in unaffected individuals.

Note: Anthropometric variations (measurements of facial form and tooth size) in HED are subtle and have not proven clinically useful; however, 3D facial recognition has shown promise [Hadj-Rabia et al 2017].

Suggestive findings for X-linked HED in heterozygous females

- Because females with X-linked HED show mosaic patterns of sweat pore function and distribution, use of an iodine solution to assess sweat gland function or impression materials to assess number and distribution of sweat pores is particularly useful.
- Between 60% and 80% of females with X-linked HED display some degree of hypodontia [Cambiaghi et al 2000].

Establishing the Diagnosis

Classic HED is often diagnosed after infancy in affected individuals with the above characteristic features of hypotrichosis, hypohidrosis, and hypodontia.

- **Male proband.** The diagnosis of classic HED **is established** in a male proband with the above characteristic features. Identification of a hemizygous *EDA* pathogenic (or likely pathogenic) variant or biallelic *EDAR*, *EDARADD*, or *WNT10A* pathogenic (or likely pathogenic) variants confirms the diagnosis.

- **Female proband.** The diagnosis of classic HED **is established** in a female proband with the above characteristic features. Identification of biallelic *EDAR*, *EDARADD*, or *WNT10A* pathogenic (or likely pathogenic) variants confirms the diagnosis.

Mild HED

- **Male proband.** The diagnosis of mild HED **can be established** in a male proband with mild manifestations of the above characteristic features. Identification of a heterozygous *EDAR*, *EDARADD*, or *WNT10A* pathogenic (or likely pathogenic) variant confirms the diagnosis.
- **Female proband.** The diagnosis of mild HED due to an *EDA* pathogenic variant **can be established** in a female proband with a mosaic pattern of sweat pore function and distribution, hypodontia, and a family history suggestive of X-linked HED. Identification of a heterozygous *EDA* pathogenic (or likely pathogenic) variant by molecular genetic testing confirms the diagnosis. The diagnosis of mild HED **can also be established** in a female with mild manifestations of the above characteristic features by identification of a heterozygous pathogenic (or likely pathogenic) variant in *EDAR*, *EDARADD*, or *WNT10A*.

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

Molecular testing approaches can include **serial single-gene testing** and a **multigene panel**.

- **Serial single-gene testing** can be considered if:
 - The proband's findings are classic and consistent with X-linked inheritance (i.e., males generally more severely affected than females, no male-to-male transmission). Sequence analysis of *EDA* is performed first, followed by gene-targeted deletion/duplication analysis of *EDA* if no pathogenic variant is found.
 - The proband's findings are classic and consistent with autosomal recessive inheritance, or mild and consistent with autosomal dominant inheritance. Sequence analysis of *EDAR*, *EDARADD*, and *WNT10A* should be performed, followed by deletion/duplication analysis if no pathogenic variant is found by sequence analysis.

If molecular genetic testing of *EDA*, *EDAR*, *EDARADD*, and *WNT10A* do not identify a pathogenic variant, other forms of ectodermal dysplasia should be considered (see Differential Diagnosis).

- **A multigene panel** that includes *EDA*, *EDAR*, *EDARADD*, *WNT10A*, and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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](#).

Table 1. Molecular Genetic Testing Used in Hypohidrotic Ectodermal Dysplasia

Gene ¹	MOI	Proportion of HED Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants ² Detectable by Method	
			Sequence analysis ³	Gene-targeted deletion/duplication analysis ⁴
<i>EDA</i>	XL	~50%-60% ⁵	~85%-90% ⁶	~10%-15% ⁶
<i>EDAR</i>	AD AR	~10%-15% ⁵	>99% ⁷	See footnote 8.
<i>EDARADD</i>	AD AR	~2%-3% ⁵	~95% ⁵	See footnote 9.
<i>WNT10A</i>	AD AR	15%-20% ⁵	~100%	None reported ¹⁰
Unknown ¹¹		~10%	NA	

NA = not applicable

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. 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](#).

4. 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.

5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

6. Monreal et al [1998], Chassaing et al [2006], Lexner et al [2008], van der Hout et al [2008], Cluzeau et al [2011]

7. Monreal et al [1999], Chassaing et al [2006], Cluzeau et al [2011], Plaisancié et al [2013]

8. A deletion of at least exon 4 was detected in one individual [Monreal et al 1999].

9. An exon 4 deletion in *EDARADD* has been reported in affected individuals from a Tunisian family [Cluzeau et al 2019].

10. To date, no large intragenic *WNT10A* deletions/duplications have been reported in individuals with HED.

11. To date, there are limited reports of individuals with features of HED and pathogenic variants in *LEF1*, *LRP6*, or *TRAF6* [Wisniewski & Trzeciak 2012, Lévy et al 2020, Yu et al 2021]. A novel disease gene mapped to a 5-cM interval at 14q12-q13.1 in one large family with autosomal dominant hypohidrotic/anhidrotic ectodermal dysplasia; *NFKBIA* was excluded by sequence analysis [Cluzeau et al 2011].

Clinical Characteristics

Clinical Description

Classic Hypohidrotic Ectodermal Dysplasia

Males with X-linked hypohidrotic ectodermal dysplasia (HED) and males and females with autosomal recessive HED caused by *EDAR* or *EDARADD* pathogenic variants have the classic form of HED.

Neonates with HED may be diagnosed because of peeling skin (like that of "postmature" babies) and periorbital hyperpigmentation. In infancy, they may be irritable because of heat intolerance; elevated body temperatures are not uncommon. More often, diagnosis is delayed until teeth fail to erupt at the expected age (6-9 months) or the teeth that erupt are conical. By this age, affected individuals may have chronic eczema and periorbital skin may appear wrinkled.

The cardinal features of HED become obvious during **childhood**:

- **Hypotrichosis.** Thin, lightly pigmented, and slow-growing scalp hair. The apparent slow growth of the scalp hair may result from the excessive fragility of the shafts, which break easily with the usual wear and tear of childhood.

- **Hypohidrosis.** Greatly reduced sweat function leading to episodes of hyperthermia until the affected individual or family acquires experience with environmental modifications to control temperature [Blüschke et al 2010, Schneider et al 2011]
- **Hypodontia.** Flat or knife-edged alveolar ridges where teeth are not developing; later-than-average appearance of only a few teeth, which are abnormally formed [Lexner et al 2008]

Other signs of classic HED include the following:

- Diminished and asymmetric development of the alveolar ridge
- Changes in nasal secretions from concretions (solidified secretions in the nasal and aural passages) in early infancy to large mucous clots thereafter
- Depressed nasal bridge that is obvious by early childhood
- Decreased sebaceous secretions
- Dry eye symptoms due to abnormal meibomian glands [Dietz et al 2013]
- Fragile-appearing skin
- Lack of dermal ridges
- Periorbital hyperpigmentation that persists
- Recurrent pneumonia and asthma-like symptoms related to abnormal bronchial glands [Dietz et al 2013]
- Raspy voice
- Midface hypoplasia

Physical growth and psychomotor development are otherwise within normal limits.

Mild Hypohidrotic Ectodermal Dysplasia

Females with X-linked HED and males and females with autosomal dominant HED typically have mild HED.

Females with X-linked HED may exhibit mild manifestations of any or all the cardinal features: some sparseness of the hair, patchy distribution of sweat dysfunction, and a few small or missing teeth [Wohlfart et al 2020]. They may also notice deficient milk production during nursing or have underdeveloped nipples.

Individuals with autosomal dominant HED exhibit mild manifestations as described for females with X-linked HED, without the patchy distribution of sweat dysfunction.

WNT10A-Related Hypohidrotic Ectodermal Dysplasia

Variable phenotypes are reported in individuals with pathogenic variants in *WNT10A*. Individuals may present with severe manifestations consistent with odonto-onycho-dermal dysplasia [Krøigård et al 2016] or Schopf-Schulz-Passarge syndrome (see Genetically Related Disorders). *WNT10A* pathogenic variants may also be found in individuals with mild HED and abnormal dentition. Individuals with *WNT10A* variants are more likely than those with other forms of HED to have missing fingernails and toenails at birth. Also, unlike other forms of HED, the deciduous dentition may be almost completely present but with abnormally shaped teeth, while there is often severe hypodontia of the adult dentition. There may be hyperhidrosis involving the palms and soles with decreased sweating on the rest of the body.

Genotype-Phenotype Correlations

EDA. Phenotypes resulting from *EDA* pathogenic variants range from classic HED to nonsyndromic hypodontia. Recent investigations suggest that most *EDA* pathogenic variants associated with nonsyndromic hypodontia are missense variants mostly located in the region encoding the tumor necrosis factor domain. Many pathogenic variants associated with X-linked HED are thought to be loss-of-function variants including nonsense variants, insertions, and deletions that span the gene [Zhang et al 2011].

EDAR. Variable phenotypes that range from mild to severe are associated with *EDAR* pathogenic variants, but genotype-phenotype correlations remain limited [Chassaing et al 2006]. The association of *EDAR* pathogenic variants and HED features along with the additional findings of amastia and palmoplantar hyperkeratosis has been reported twice, once with the novel homozygous variant c.803+1G>A [Mégarbané et al 2008] and once with the novel homozygous missense variant c.338G>A (p.Cys113Tyr) [Haghighi et al 2013].

WNT10A. Variable phenotypes are reported in individuals with pathogenic variants in *WNT10A*. Homozygosity for the common c.321C>A (p.Cys107Ter) nonsense variant may be identified more frequently in individuals with severe manifestations, including odonto-onycho-dermal dysplasia [Krøigård et al 2016]. *WNT10A* pathogenic variants may also be found in individuals with abnormal dentition in association with additional mild ectodermal symptoms or with selective tooth agenesis [Mues et al 2014, Bergendal et al 2016].

Penetrance

Penetrance is not well described for most ectodermal dysplasias.

Nomenclature

Historically, the term "anhidrotic" has been defined as the inability to perspire; "hypohidrotic" suggests impairment in the ability to perspire. Because most individuals with HED have at least a limited ability to perspire, the term "hypohidrotic" more accurately reflects the condition.

Prevalence

Although not specifically known, it is estimated that at least one in 5,000-10,000 newborns has HED. This is probably an underestimate of the prevalence, as many individuals may be missed during infancy before the cardinal features become obvious.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *EDA*, *EDAR*, *EDARADD*, and *WNT10A* are summarized in Table 2.

Table 2. Allelic Disorders

Gene	Disorder
<i>EDA</i>	Isolated hypodontia (OMIM 313500)
<i>EDAR</i>	Isolated oligodontia [Zhou et al 2021]
<i>EDARADD</i>	Isolated oligodontia [Arte et al 2013]
<i>WNT10A</i>	Schopf-Schulz-Passarge syndrome (OMIM 224750) ¹
	Odonto-onycho-dermal dysplasia (OMIM 257980) ¹
	Selective tooth agenesis (OMIM 150400)

1. Schopf-Schulz-Passarge syndrome and odonto-onycho-dermal dysplasia syndrome (both associated with additional and/or more severe features) represent the most severe end of the *WNT10A*-related ectodermal dysplasia spectrum.

Differential Diagnosis

Numerous types of ectodermal dysplasia exist [Wright et al 2019]. Hypodontia with a vague history of heat intolerance or slight sparseness of the hair is particularly common and includes a broad differential diagnosis.

The presence of onychodysplasia (inherent abnormalities of nail development) and other developmental abnormalities favor diagnoses other than hypohidrotic ectodermal dysplasia (HED).

Ectodermal dysplasias that need to be considered in the differential diagnosis of HED are summarized in Table 3.

Table 3. Ectodermal Dysplasias in the Differential Diagnosis of Hypohidrotic Ectodermal Dysplasia

Gene(s)	Disorder	MOI	Clinical Characteristics				
			Hair	Skin	Dental	Nails	Other
<i>DLX3</i>	Trichodontoosseous syndrome (OMIM 190320)	AD	Kinky or curly hair	Normal sweating ability	Thin enamel, small, widely spaced teeth, teeth pits, & taurodontism	Brittle nails	↑ bone density
<i>GJB2</i>	Keratitis-ichthyosis-deafness syndrome (OMIM 148210)	AD	Sparse hair	Progressive palmoplantar hyperkeratosis	NR	Nail dystrophy	Sensorineural deafness, photophobia, & corneal ulceration
<i>GJB6</i>	Hidrotic ectodermal dysplasia 2	AD	Sparse hair or alopecia	Normal sweating ability, palmoplantar hyperkeratosis	Normal teeth	Nail dystrophy	Photophobia
<i>HOXC13</i>	Ectodermal dysplasia 9, hair/nail type (OMIM 614931)	AR	Hypotrichosis	NR	Normal teeth	Nail dystrophy	
<i>IKBKG</i>	Hypohidrotic ectodermal dysplasia w/immunodeficiency (OMIM 300291)	XL	Sparse hair	Hypohidrosis	Hypodontia	NR	Impaired immune function w/risk for recurrent infections, hypogammaglobulinemia, T cell dysfunction
	Incontinentia pigmenti	XL	Atrophic hair	Normal sweating ability, 4-stage skin rash, ¹ pigmentary involvement	Hypodontia	Nail dystrophy	Cataract, microphthalmia, retinal vascular proliferation, & other ocular abnormalities, breast hypoplasia or aplasia, short stature
<i>KRT74</i>	Ectodermal dysplasia 7, hair/nail type (OMIM 614929)	AR	Hypotrichosis	NR	Normal teeth	Nail dystrophy	
<i>KRT85</i>	Ectodermal dysplasia 4, hair/nail type (OMIM 602032)	AR	Hypotrichosis	NR	Normal teeth	Nail dystrophy	
<i>MSX1</i>	Witkop tooth & nail syndrome (OMIM 189500)	AD	Normal hair	Normal sweating ability	Partial to total absence of permanent teeth	Thin, small, & friable nails, nail pits & ridging	
<i>NFKBIA</i>	Anhidrotic ectodermal dysplasia w/T cell immunodeficiency (OMIM 612132)	AD	Sparse hair	Hypohidrosis, cutaneous candidiasis	Hypodontia	NR	Impaired immune function w/risk for recurrent infections, hypogammaglobulinemia

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics				
			Hair	Skin	Dental	Nails	Other
<i>TSPEAR</i>	Ectodermal dysplasia 14 (OMIM 618180)	AR	Hypotrichosis of scalp, esp anterior	Variable hypohidrosis	Hypodontia	NR	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NR = not reported; XL = X-linked

1. Incontinentia pigmenti manifests in stages that evolve sequentially: stage I (bullous), stage II (verrucous), stage III (hyperpigmentation), and stage IV (atretic). The onset and duration of each stage vary among individuals, and not all individuals experience all four stages.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hypohidrotic ectodermal dysplasia (HED), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Hypohidrotic Ectodermal Dysplasia

System/Concern	Evaluation	Comment
Hair	Assess severity of hypotrichosis.	
Skin	Assess severity of hypohidrosis incl episodes of hyperthermia.	
Dental	Dental eval to assess jaws, alveolus, & developing dentition by age 1 yr	Typically by palpating dental alveolus to establish if developing tooth buds (which manifest as bulges in alveolus) are present
	Panoramic or conventional dental radiographs	As needed to determine extent of hypodontia & inform treatment planning
ENT	Assess for solidified secretions in nasal & aural passages.	
Eyes	Ophthalmologic eval	To assess for dry eyes due to abnormal meibomian glands
Respiratory	Assess for recurrent pneumonia & asthma related to abnormal bronchial glands.	
Genetic counseling	By genetics professionals ¹	To inform affected persons & their families re nature, MOI, & implications of HED to facilitate medical & personal decision making

HED = hypohidrotic ectodermal dysplasia; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management of affected individuals targets the three cardinal features of HED (hypotrichosis, hypohidrosis, and hypodontia) and is directed at optimizing psychosocial development, establishing optimal oral function, and preventing hyperthermia (see Table 5).

Table 5. Treatment of Manifestations in Individuals with Hypohidrotic Ectodermal Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Hypotrichosis	Wigs or special hair care formulas & techniques to manage sparse, dry hair	1 report describes a child w/HED & alopecia who was treated w/topical minoxidil to scalp & had resultant hair growth. ¹
Hypohidrosis	<ul style="list-style-type: none"> • During hot weather: access to adequate water supply & cool environment (e.g., air conditioning, wet T-shirt, &/or spray bottle of water) ² • Skin care products for mgmt of dry skin, eczema, & rashes assoc w/certain outdoor exposures (e.g., swimming) 	Some persons may benefit from cooling vests.
Hypodontia	<ul style="list-style-type: none"> • Dental treatment, ranging from simple restorations to dentures, should begin at early age. • Treatments incl restorations, bonding of conical teeth, dental implants, &/or dentures. • Orthodontics may be necessary. • Dietary counseling for those persons who have trouble chewing & swallowing despite adequate dental care 	<ul style="list-style-type: none"> • Bonding of conical teeth improves aesthetics & chewing ability. • Dental implants in anterior portion of mandibular arch have proven successful only in children age ≥7 yrs. ³ • Children w/HED typically need dental prostheses replaced every 2.5 yrs. • Dental implants in adults can support aesthetic & functional dentition.
Hyposalivation	<ul style="list-style-type: none"> • Therapeutics (e.g., saliva substitutes) directed at maintaining oral lubrication & to ↓ risk of dental caries • Fluoride treatments as recommended by dentist • Consider other dental caries preventive approaches such as pit & fissure sealants. 	
Solidified nasal & aural secretions	<ul style="list-style-type: none"> • Mgmt per ENT physician • Removal of nasal & aural concretions w/suction devices or forceps • Humidification of ambient air to prevent their formation 	
Dry eyes	Lubrication eye drops	
Respiratory manifestations	<ul style="list-style-type: none"> • Mgmt of recurrent respiratory infections & asthma per primary care provider • Referral to allergist &/or pulmonologist as needed for more significant respiratory manifestations 	

1. Lee et al [2013]

2. Affected individuals learn to control their exposure to heat and to minimize its consequences, but special situations may arise in which intervention by physicians and families is helpful. For example, a physician may have to prescribe an air conditioner before a school district complies, or parents may have to advocate for children who need to carry liquids into areas where they are prohibited.

3. Kramer et al [2007], Stanford et al [2008]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 6 are recommended.

Table 6. Recommended Surveillance for Individuals with Hypohidrotic Ectodermal Dysplasia

System/Concern	Evaluation	Frequency
Integument	Assess severity & treatment response for hypotrichosis & hypohidrosis.	Annually &/or as needed
Dental	Dental exam to monitor tooth & maxillary/mandibular development, provide anticipatory guidance for parents, monitor existing treatments, & provide continued interventions as needed	Every 6-12 mos beginning at age 1 yr
ENT	Assess for abnormal nasal & aural secretions.	Annually &/or as needed
Eyes	Ophthalmologic eval to assess for dry eyes due to abnormal meibomian glands	
Respiratory	Assess for recurrent pneumonia & asthma related to abnormal bronchial glands.	

Agents/Circumstances to Avoid

Individuals with severe hypohidrosis can have marked heat intolerance; care should be taken to prevent exposure to extreme heat and the potential for febrile seizures.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and treatment and, importantly, measures to avoid hyperthermia. Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Targeted history, physical examination, and dental examination for the features of HED if the pathogenic variant(s) in the family are not known. Testing for hypohidrosis (see Suggestive Findings) can be done in at-risk relatives of an individual with X-linked HED.

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

Pregnancy Management

Optimal prenatal nutrition is recommended for mothers who are unaffected heterozygotes or are affected with HED. Affected women at risk for hyperthermia should take extra care not to become overheated during pregnancy. There are no other special recommendations for pregnancy management.

Some women may have difficulty breastfeeding their infants because of hypoplasia of the mammary glands.

Therapies Under Investigation

A Phase II clinical trial was conducted at several US and European medical centers to investigate the use of EDI200, developed by Edimer Pharmaceuticals, Inc [Huttner 2014]. The results of the study were inconclusive. EDI200 is an ectodysplasin-A1 (EDA-A1) replacement protein (Fc-EDA) that has been shown to bind specifically to the EDA-A1 receptor (EDAR) and activate the signaling pathway that leads to normal ectodermal development. EDI200 has demonstrated permanent correction of the disease manifestations in both mouse and dog models of X-linked HED, with reduction in mortality and morbidity [Huttner 2014, Körber et al 2020]. Postnatal administration of EDI200 did not change the HED phenotype, and a prenatal administration approach of the protein was adopted.

Schneider et al [2018] reported successful treatment of X-linked HED via intra-amniotic administration of the recombinant protein, Fc-EDA, to two affected male twins at gestational weeks 26 and 31 and to a single affected male fetus at week 26. Postnatally, they were able to sweat normally and had not developed X-linked HED-

related hyperthermia or respiratory illnesses by age 14 and 22 months. Longer-term follow up of these boys has shown continued good outcomes, although correction of the deciduous dentition was not achieved. They are predicted to have more permanent teeth than would have been expected for classic X-linked HED. An additional three male fetuses have been treated since that report through a compassionate use program [Holm Schneider, personal communication].

Subsequently, an open-label, prospective, genotype-match controlled non-randomized, multicenter, international Phase II clinical trial has begun recruiting to investigate the efficacy and safety of ER004 (previously known as EDI200) administered intra-amniotically as a prenatal treatment for males with X-linked HED. The aim of the trial is to confirm the efficacy and safety of ER004 administered intra-amniotically in a larger cohort. The target population will consist of male fetuses diagnosed with X-linked HED based on identification of a heterozygous *EDA* pathogenic variant in the mother and ultrasonographic identification of a significantly reduced number of fetal tooth germs, or by identification of a hemizygous *EDA* pathogenic variant in the fetus. The mother will receive three doses of ER004 intra-amniotically in the late second and the third trimesters of pregnancy. Efficacy and safety will be assessed in the affected males up to age six months and safety will be assessed in the mothers up to one month following delivery. In the long-term follow-up phase, efficacy and safety will be assessed in affected males up to age five years. Sweating ability of affected males will be compared to an untreated relative, when available, or to a matched control from a previous natural history study.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://european-clinical-trials-register.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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

Hypohidrotic ectodermal dysplasia (HED) caused by pathogenic variants in *EDA* is inherited in an X-linked manner.

EDAR-, *EDARADD*-, and *WNT10A*-related HED are inherited in an autosomal recessive or an autosomal dominant manner.

X-Linked HED – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for the *EDA* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a female has more than one affected child and no other affected relatives and the *EDA* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo* *EDA* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.

- Clinical examination may detect manifestations of X-linked HED in the mother; manifestations in heterozygous females are typically milder than those seen in affected males (see Clinical Description, Mild HED).
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment. Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Parents of a female proband

- A female proband may have inherited the *EDA* pathogenic variant from her father (who is expected to be affected) or her mother (who may be mildly affected), or the pathogenic variant may be *de novo*.
- Clinical examination may clarify the status of the parents. Molecular genetic testing of both parents is recommended to confirm their genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband.

The risk to sibs depends on the genetic status of the mother:

- If the mother is heterozygous for an *EDA* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may show manifestations of ectodermal dysplasia (see Clinical Description, Mild HED).
- If the proband represents a simplex case and the *EDA* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

Sibs of a female proband.

The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has an *EDA* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may show manifestations of ectodermal dysplasia (see Clinical Description, Mild HED).
- If the father of the proband has an *EDA* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case and if the *EDA* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a male proband. Affected males transmit the *EDA* pathogenic variant to all of their daughters and none of their sons.

Offspring of a female proband. Heterozygous females have a 50% chance of transmitting the *EDA* pathogenic variant to each child.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has a pathogenic variant, the parent's family members may be at risk.

Heterozygote detection. Molecular genetic identification of female heterozygotes requires prior identification of the *EDA* pathogenic variant in the family.

Detection of heterozygotes based on clinical findings is often imprecise. If sweat distribution is patchy or many teeth are absent, establishing genetic status is relatively easy. Otherwise, mild manifestations in females with X-linked HED overlap with features in the general population. Hypodontia, for instance, is relatively common in the general population, and absence of one or two teeth in the mother of an affected male may be coincidental. Furthermore, there are no useful standards to judge hair density, and reports of sweat dysfunction, often judged

by heat intolerance, can be inaccurate. Computerized facial recognition appears to be relatively insensitive in heterozygote detection as well.

Autosomal Recessive HED – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive HED are presumed to be heterozygous for a pathogenic variant in *EDAR*, *EDARADD*, or *WNT10A*.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
 - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
 - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes may have mild features of the disorder (see Clinical Description, Mild HED), especially individuals heterozygous for a *WNT10A* pathogenic variant [Doolan et al 2021].

Sibs of a proband

- If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes may have mild features of the disorder (see Clinical Description, Mild HED), especially individuals heterozygous for a *WNT10A* pathogenic variant [Doolan et al 2021].

Offspring of a proband. The offspring of an individual with autosomal recessive HED are obligate heterozygotes for a pathogenic variant in *EDAR*, *EDARADD*, or *WNT10A*.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant.

Heterozygote detection. Heterozygote detection for at-risk relatives requires prior identification of the *EDAR*, *EDARADD*, or *WNT10A* pathogenic variants in the family.

Autosomal Dominant HED – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant HED have an affected parent.
- An individual diagnosed with autosomal dominant HED may have the disorder as the result of a *de novo* *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant. The proportion of probands who have a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include physical examination and molecular genetic testing for the *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant identified in the proband.

- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
 - The proband has a *de novo* pathogenic variant.
 - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with autosomal dominant HED 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 molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to sibs 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 of inheriting the pathogenic variant is 50%.
- If the *EDAR*, *EDARADD*, or *WNT10A* 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].

Offspring of a proband. Each child of an individual with autosomal dominant HED has a 50% chance of inheriting the *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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, are heterozygous, or are at risk of being heterozygous.

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 *EDA*, *EDAR*, *EDARADD*, or *WNT10A* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for HED 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

- **MedlinePlus**

[Hypohidrotic ectodermal dysplasia](#)

- **National Foundation for Ectodermal Dysplasias (NFED)**

Phone: 618-566-2020

Email: info@nfed.org

www.nfed.org

- **Selbsthilfegruppe Ektodermale Dysplasie e.V.**

Consumer health-oriented organization for Germany, Austria, and Switzerland

Germany

Phone: 7127 969691

Email: andrea@ektodermale-dysplasie.de

www.ektodermale-dysplasie.de

- **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. Hypohidrotic Ectodermal Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>EDA</i>	Xq13.1	Ectodysplasin-A	EDA @ LOVD	EDA	EDA
<i>EDAR</i>	2q13	Tumor necrosis factor receptor superfamily member EDAR	EDAR database	EDAR	EDAR

Table A. continued from previous page.

EDARADD	1q42.3-q43	Ectodysplasin-A receptor-associated adapter protein	EDARADD database	EDARADD	EDARADD
WNT10A	2q35	Protein Wnt-10a	WNT10A database	WNT10A	WNT10A

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 Hypohidrotic Ectodermal Dysplasia ([View All in OMIM](#))

129490	ECTODERMAL DYSPLASIA 10A, HYPOHIDROTIC/HAIR/NAIL TYPE, AUTOSOMAL DOMINANT; ECTD10A
224900	ECTODERMAL DYSPLASIA 10B, HYPOHIDROTIC/HAIR/TOOTH TYPE, AUTOSOMAL RECESSIVE; ECTD10B
300451	ECTODYSPLASIN A; EDA
305100	ECTODERMAL DYSPLASIA 1, HYPOHIDROTIC, X-LINKED; XHED
604095	ECTODYSPLASIN A RECEPTOR; EDAR
606268	WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 10A; WNT10A
606603	EDAR-ASSOCIATED DEATH DOMAIN; EDARADD
614941	ECTODERMAL DYSPLASIA 11B, HYPOHIDROTIC/HAIR/TOOTH TYPE, AUTOSOMAL RECESSIVE; ECTD11B

Molecular Pathogenesis

EDA encodes ectodysplasin-A (EDA), a protein that is important for normal development of ectodermal appendages including hair, teeth, and sweat glands. EDA is important in the NFKappaB pathway, which involves numerous downstream genes involved in embryogenesis. EDA binds to the ectodysplasin-A receptor (EDAR; encoded by *EDAR*) activating the NFKappaB pathway. Mutated EDA is unable to bind and activate the pathway.

EDAR contains a single transmembrane domain with type 1 membrane topology. The protein probably functions as a multimeric receptor and is related to the TNFR family. Mutated EDAR is unable to bind with ectodysplasin. *EDAR* variants causing autosomal recessive hypohidrotic ectodermal dysplasia (HED) exhibit loss of function, while those associated with autosomal dominant HED exhibit a dominant-negative effect [Valcuende-Cavero et al 2008]. At least two of the dominant-negative pathogenic variants are not associated with the HED phenotype.

The protein encoded by *EDARADD* is similar to the death domain, MyD88, a cytoplasmic transducer of Toll/interleukin receptor signaling [Headon et al 2001]. It also contains a Traf-binding consensus sequence. It is coexpressed with tumor necrosis factor receptor superfamily member EDAR in epithelial cells during the formation of hair follicles and teeth. It interacts with the death domain of EDAR and links the receptor to signaling pathways downstream. *EDARADD* pathogenic variants alter the charge of an amino acid in the protein, usually rendering it unable to interact with EDAR. In one family with autosomal dominant HED, a novel missense variant did not interfere with interaction between EDAR and *EDARADD* proteins but still led to impaired activation of NFKappaB signaling [Wohlfart et al 2016, Asano et al 2021].

WNT10A encodes a peptide containing two N-linked glycosylation sites and residues conserved among WNTs. The protein contains two domains, a signal peptide and the Wnt domain, and encodes a secreted signaling molecule that is involved in several developmental processes, such as regulation of cell fate and patterning during embryogenesis. *WNT10A* and *WNT10B* are highly expressed in embryonic skin as well as the placodes involved in follicle morphogenesis. *WNT10A* is also very important for normal dentinogenesis and tooth morphogenesis.

Mechanism of disease causation. Depending on the specific variant and resulting protein, the mechanism of disease can be loss of function or a dominant-negative effect. *EDA* pathogenic variants are loss of function. Pathogenic variants in *WNT10A* appear to cause changes in protein folding or stabilization causing a loss of function [Zeng et al 2021]. *EDARADD* pathogenic variants can result in a dominant-negative effect or loss of function depending on the variant [Asano et al 2021].

Gene-specific laboratory considerations: *EDARADD*. *EDARADD* has two isoforms, each w/6 exons encoding 205 & 215 amino acid proteins (NM_080738.3 and NM_145861.2, respectively).

Table 7. Hypohidrotic Ectodermal Dysplasia: Notable Pathogenic Variants by Gene

Gene ¹	Reference Sequences	DNA Nucleotide Change (Alias ²)	Predicted Protein Change	Comment [Reference]
<i>EDAR</i>	NM_022336.4 NP_071731.1	c.338G>A	p.Cys113Tyr	Assoc w/HED & addl findings of amastia & palmoplantar hyperkeratosis [Haghighi et al 2013]
	NM_022336.4	c.803+1G>A (IVS9+1G>A)	--	Assoc w/HED & addl findings of amastia & palmoplantar hyperkeratosis [Mégarbané et al 2008]
<i>WNT10A</i>	NM_025216.3 NP_079492.2	c.321C>A	p.Cys107Ter	One of the most common <i>WNT10A</i> pathogenic variants

HED = hypohidrotic ectodermal dysplasia

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.

1. Genes from Table 1 in alphabetic order

2. Variant designation that does not conform to current naming conventions

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Revision History

- 27 October 2022 (sw) Comprehensive update posted live
- 1 June 2017 (sw) Comprehensive update posted live
- 15 May 2014 (me) Comprehensive update posted live
- 13 June 2013 (aa) Revision: *EDAR* deletion reported
- 29 December 2011 (me) Comprehensive update posted live
- 23 July 2009 (me) Comprehensive update posted live
- 16 November 2006 (me) Comprehensive update posted live
- 28 April 2003 (me) Review posted live
- 23 October 2002 (rj) Original submission

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