GENEReviews

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Focal Dermal Hypoplasia

[*Goltz Syndrome; Goltz-Gorlin Syndrome*]

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Summary

Disease characteristics. Focal dermal hypoplasia is a multisystem disorder characterized primarily by involvement of the skin, skeletal system, eyes, and face. Skin manifestations present at birth include atrophic and hypoplastic areas of skin; cutis aplasia; fat nodules in the dermis manifesting as soft, yellow-pink cutaneous nodules; and pigmentary changes. Verrucoid papillomas of the skin and mucous membranes may appear later. The nails can be ridged, dysplastic, or hypoplastic; hair can be sparse or absent. Limb malformations include oligo/syndactyly and split hand/foot. Developmental abnormalities of the eye can include anophthalmia/microphthalmia, iris and chorioretinal coloboma, and lacrimal duct abnormalities. Craniofacial findings can include facial asymmetry, notched alae nasi, cleft lip and palate, and pointed chin. Occasional findings include dental anomalies, abdominal wall defects, diaphragmatic hernia, and renal anomalies. Psychomotor development is usually normal; some individuals have cognitive impairment.

Diagnosis/testing. Diagnosis is based on clinical findings and molecular genetic testing. *PORCN* is the only gene known to cause focal dermal hypoplasia. Sequence analysis and testing for large gene deletions are available on a clinical basis.

Management.*Treatment of manifestations:* care by a dermatologist for painful and pruritic erosive lesions that are prone to infection; referral to an otolaryngologist for evaluation of large papillomas of the larynx and management with surgical or laser therapy; referral to a physical/occupational therapist and hand surgeon for management of hand and foot malformations; standard protocols for management of diaphragmatic hernia and abdominal wall defects, and structural abnormalities of the eyes and kidneys. *Prevention of secondary complications:* preventative dental care for those with enamel hypoplasia to reduce the risk for dental caries. *Surveillance:* routine follow-up with a dermatologist; preoperative evaluation by an otolaryngologist for hypopharyngeal and/or tonsillar papillomas; routine evaluations for scoliosis, particularly in individuals with costovertebral segmentation abnormalities.

Genetic counseling. Focal dermal hypoplasia is inherited in an X-linked dominant manner. Females (90% of affected individuals) are heterozygous or mosaic for mutations in *PORCN*; live-born affected males (10% of affected individuals) are mosaic for mutations in *PORCN*. It is presumed that non-mosaic hemizygous males are not viable. Approximately 95% of females with focal dermal hypoplasia have a new gene mutation; approximately 5% inherited the mutation from a parent. The risk that the mutant *PORCN* allele will be transmitted by an affected female with a heterozygous mutation is 50%; however, most male conceptuses with

the mutant *PORCN* allele are presumed to be spontaneously aborted. Thus, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males. If the affected female has a mosaic mutation, the risk to her female offspring of inheriting the mutation is as high as 50%, depending on the level of mosaicism in her germline. Prenatal testing is possible for pregnancies at increased risk if the disease-causing mutation in the family has been identified.

Diagnosis

Clinical Diagnosis

Focal dermal hypoplasia is a multisystem disorder primarily involving the skin, skeletal system, eyes, and face. The diagnosis of focal dermal hypoplasia should be considered in individuals with **either** of the following:

- Multiple skin manifestations
- One typical skin manifestation in conjunction with characteristic limb malformations

Skin manifestations include the following (see Figure 1 and Figure 2):

- Atrophic and hypoplastic areas of skin that often follow the lines of Blaschko and appear as depressed regions of pink or white color, often with a fibrous texture.

  Note: The lines of Blaschko correspond to cell migration pathways evident during embryonic and fetal skin development. Like dermatomes, the lines of Blaschko are linear on the limbs and circumferential on the trunk. Unlike dermatomes, the lines of Blaschko do not correspond to innervation patterns.
- Hypo- or hyperpigmented changes that usually follow the lines of Blaschko
- Cutis aplasia that may occur on the scalp or any part of the body
- Soft, yellow-pink nodules on the skin (which represent fat nodules in the dermis) that are typically seen on the trunk and extremities
- Verrucoid papillomas of the skin and mucous membranes
- Ridged and dysplastic (abnormal)/hypoplastic (small) nails
- Sparse or absent hair on the scalp and in areas of abnormal skin on the body (may be present at birth and may evolve with time)
- Telangiectases (may be seen on the face, trunk, and extremities)

Limb malformations include the following (see Figure 3):

- Oligodactyly (fewer than five digits on a hand or foot) and/or syndactyly (joining or webbing of two or more fingers or toes) which may be seen in one or both hands or feet. Central digits are more frequently involved.
- Split hand/foot malformation that may occur on one or more extremities

When the diagnosis of focal dermal hypoplasia is unclear, a skeletal survey may be helpful to evaluate for the following:

- Osteopathia striata, a striated appearance of the bones evident on plain x-rays and of no clinical or medical significance [Larrègue et al 1972]. It is not clear if the striations reflect increased or decreased bone density.

- Costovertebral segmentation abnormalities, including fused ribs, bifid ribs, hemivertebrae, and/or butterfly vertebrae

The diagnosis of focal dermal hypoplasia should be confirmed by molecular genetic testing.

Testing

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene.*PORCN* is the only gene known to cause focal dermal hypoplasia:

- Affected females are heterozygous for a *PORCN* mutation or have somatic mosaicism for a *PORCN* mutation.
- Affected males have somatic mosaicism for *PORCN* mutations [Grzeschik et al 2007, Wang et al 2007].

Other loci. Only 80% (12/16 females and 4/4 males) of individuals with a clinical diagnosis of focal dermal hypoplasia in one study had mutations in *PORCN* [Wang et al 2007]; however, phenotypic information was limited. The diagnosis in those without mutations in *PORCN* could not be confirmed, even though two were described by the referring clinician as "typical" focal dermal hypoplasia. Another study of individuals with better-characterized phenotypes found mutations in all (16/16) females. No evidence suggesting locus heterogeneity exists at this time.

Clinical testing

Sequence analysis. In limited studies, direct sequencing of PCR-amplified coding exons and microarray or quantitative PCR of *PORCN* identified a mutation or deletion in 88% of females (28/32) and 100% of males (4/4) suspected of having focal dermal hypoplasia [Grzeschik et al 2007, Wang et al 2007].

Deletion analysis

- FISH using a locus-specific bacterial artificial chromosome (BAC) probe detects typical *PORCN* deletions. Reported deletions have been large genomic deletions up to 219 kb [Wang et al 2007].
- Array-based comparative genomic hybridization (array CGH) can detect full or partial deletions of *PORCN*. Probes covering *PORCN* may be included on CGH arrays designed for clinical diagnosis.

Research testing

Deletion/duplication analysis. Quantitative PCR to detect exonic, multiexonic, and whole-gene deletions is available on a research basis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Focal Dermal Hypoplasia

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]		Test Availability
			Females	Males	
PORCN	Sequence analysis	Small deletions and duplications; missense and nonsense mutations; insertions	23/32 (72%)	4/4 (100%) [2]	Clinical Testing
	Deletion analysis [3]	Large deletions	5/32 (16%)	0	Clinical [4]

[1] Estimates based on small number of individuals [Grzeschik et al 2007, Wang et al 2007]

[2] All males tested thus far have been mosaic for mutations in *PORCN*.

[3] Using array CGH or FISH

[4] For a list of laboratories offering array CGH, see Testing.

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- Females may be mosaic for mutations in *PORCN*. In sequence analysis, mosaicism for a missense or other non-frameshifting mutation can be difficult to detect and may produce a false negative test result [Grzeschik et al 2007].
- All males tested thus far have been mosaic for mutations in *PORCN*. In sequence analysis, mosaicism for a missense or other non-frameshifting mutation can be difficult to detect and may produce a false negative test result [Wang et al 2007].

Testing Strategy

To confirm the diagnosis in a female proband

1. Perform sequence analysis.
2. If no mutation is identified on sequence analysis, test for large deletions using (e.g.) FISH or array CGH.

To confirm the diagnosis in a male proband

- Sequence analysis should be the only molecular genetic testing performed.
- No male has been reported to have a large deletion.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

According to Van Allen & Myhre (1991), Van Allen-Myhre syndrome is either a severe form of or allelic to focal dermal hypoplasia [Hancock et al 2002].

Angiomia serpiginosum has been hypothesized to be allelic to focal dermal hypoplasia [Blinkenberg et al 2007].

Clinical Description

Natural History

Focal dermal hypoplasia is a multisystem disorder caused by developmental abnormalities in mesodermal and ectodermal structures and thus primarily involves the skin, skeletal system,

eyes, and face. The manifestations vary among affected individuals and many have only a subset of the characteristic features. Nearly all individuals have at least a few of the skin manifestations.

Females account for 90% of individuals with focal dermal hypoplasia. Affected males have somatic mosaicism for mutations in *PORCN* and are generally more mildly affected than females [Grzeschik et al 2007, Wang et al 2007].

Affected females

Skin manifestations. The most characteristic features of focal dermal hypoplasia are the skin manifestations. The cutaneous findings typically follow the lines of Blaschko, cell migration pathways that are linear on the limbs and circumferential on the trunk. Hypoplastic areas are usually evident at birth; the distribution and severity may change over time.

Papillomas are typically not present at birth but develop with age. Common sites for verrucoid papillomas include around the mouth and nose, in the esophagus and larynx (where they may cause obstruction), and in the genital and anal region (where they may be confused with genital warts).

Other integumentary system findings include hypodontia of both primary and secondary dentition, along with vertical grooving of the teeth and enamel hypoplasia, which increases the risk for caries [Balmer et al 2004].

Skeletal system. Most females with focal dermal hypoplasia have limb malformations noted at birth, including syndactyly, oligodactyly, and split-hand/foot malformation [Gorlin et al 1963, Goltz et al 1970]. These malformations, which do not change over time, may impair function.

Less common limb malformations that may be present at birth and impair function include camptodactyly (contraction deformities of the digits) and reduction defects of the long bones, such as transverse deficiency of distal radius/ulna or tibia/fibula.

Osteopathia striata, a striated appearance of the bones evident on plain x-rays, is common and may be seen in childhood, adolescence, and adulthood.

Giant cell-like tumors of long bones, reported on occasion, may develop in childhood, adolescence, or adulthood. They typically become evident when a pathologic bone fracture occurs at the site of the lesion [Selzer et al 1974, Joannides et al 1983, Tanaka et al 1990]. In the small number of reports to date, none of these tumors has been malignant.

Costovertebral segmentation abnormalities, including fused ribs, bifid ribs, and hemivertebrae and butterfly vertebrae, are present at birth but are often not evident on physical examination and may only be seen on x-ray of the chest and/or spine. Although these malformations do not typically cause problems in infancy or early childhood, they may cause scoliosis as the child grows. More often, these segmentation abnormalities do not cause health issues.

Diastasis pubis, an abnormal separation of the symphysis pubis, may be an incidental finding or may present in adolescence or adulthood with pain. The gap between the pubic bones in the average non-pregnant adult is 4-5 mm. An abnormal gap is considered to be 1 cm or more, sometimes with the two bones being slightly out of alignment. In some individuals with focal dermal hypoplasia, diastasis pubis may cause pain with walking or in the symphysis pubis, legs, groin, and lower abdomen.

Fibrous dysplasia of bone (i.e., replacement of medullary bone with trabeculae of woven bone containing fluid-filled cysts embedded in a fibrous matrix) may affect any bone at any time. On x-ray the bone appears radiolucent, with what is classically described as a "ground-glass" appearance. Fibrous dysplasia may be asymptomatic or become evident when it is the site of a pathologic fracture.

Eye findings. Developmental abnormalities of the eyes are common and are evident at birth. Depending on the severity of the manifestations, vision can range from normal to blindness. Reported eye abnormalities include the following [Gorlin et al 1963, Goltz et al 1970]:

- Anophthalmia/microphthalmia (see Anophthalmia/Microphthalmia Overview)
- Microcornea
- Iris and chorioretinal coloboma
- Lacrimal duct abnormalities
- Cataracts (cortical and subcapsular)

Strabismus and/or nystagmus can be observed when visual impairment in infancy is significant.

Craniofacial findings. Facial features are variable and include facial asymmetry, notched alae nasi, pointed chin, and small underfolded pinnae. These facial characteristics are not typically evident at birth but develop with time (see Figure 4) [Gorlin et al 1963,Goltz et al 1970].

Cleft lip and palate can be present and may lead to difficulty with feeding. More severe facial clefting can cause feeding, breathing, and vision problems, as well as significant cosmetic concerns [Ascherman et al 2002].

Dental. Oral manifestations are seen in over half of affected individuals. Enamel hypoplasia that predisposes to dental caries is the most common problem. Other abnormalities include problems with the eruption, position, and number of teeth. Structural abnormalities include ridging of the teeth, microdontia (small teeth), taurodontia (prism-shaped molars), fused teeth, and abnormal root morphology [Tejani et al 2005].

Gastrointestinal. Developmental abnormalities of the digestive system are rare but may have severe consequences. These are typically evident at birth (abdominal wall defects) or cause significant problems with breathing or feeding (diaphragmatic hernia) (see Congenital Diaphragmatic Hernia Overview).

Severe gastroesophageal reflux (GER) has been reported in infancy and childhood, leading to feeding difficulties with frequent vomiting and/or discomfort/distress. The GER likely results from esophageal papillomas [Brinson et al 1987].

Other. Structural abnormalities of kidneys and urinary system that may lead to recurrent urinary tract infections and urinary reflux include the following:

- Absent kidney
- Fused/horseshoe kidney [Suskan et al 1990]

Most affected individuals with focal dermal hypoplasia are reported to be small at birth and have mild short stature, although this has been poorly characterized [Goltz et al 1970].

Development is usually normal; some individuals with focal dermal hypoplasia may have cognitive impairment. Structural brain abnormalities and spina bifida [Goltz et al 1970, Almeida et al 1988] have been reported but are uncommon.

Mixed conductive and sensorineural hearing loss has been reported on occasion.

Affected males

Because so few affected males have been reported, no data exist about a "typical" male phenotype. Affected males may have any of the features seen in affected females including typical skin findings; sparse, brittle hair; nail dystrophy; microphthalmia; syndactyly; split-hand/foot malformation; costovertebral segmentation abnormalities; osteopathia striata; and diastasis pubis [Wang et al 2007].

Pathology

Histopathologic and ultrastructural studies of the skin have shown the following:

- A thinned dermis with disordered connective tissue and decreased number of collagen bundles and elastin fibers [Kanitakis et al 2003]
- Rests of mature adipose tissue scattered throughout the reticular and papillary dermis [Howell & Freeman 1989, del Carmen Boente et al 2007]; whether these represent herniation of fat into a thinned dermis or ectopic aggregation of fat within a dysplastic dermis is unclear [Howell & Freeman 1989]
- Verrucoid papillomas that resemble squamous papillomas with hyperplastic, stratified squamous epithelium overlying a fibrovascular core. Verrucoid papillomas lack the typical morphologic evidence of human papilloma virus infection and stain negative for Epstein-Barr virus RNA [Rosen & Bocklage 2005].

Genotype-Phenotype Correlations

Information on genotype-phenotype correlations in focal dermal hypoplasia is limited.

Available data suggest that neither the mutation nor the level of X-chromosome inactivation correlates with severity of the phenotype [Grzeschik et al 2007, Wang et al 2007].

Note: All females with deletions in *PORCN* have extremely skewed X-chromosome inactivation, whereas most females with point mutations have random X-chromosome inactivation [Grzeschik et al 2007, Wang et al 2007].

All males reported to date are mosaic for mutations in *PORCN* and are generally more mildly affected than females.

Penetrance

Focal dermal hypoplasia appears to be fully penetrant in females; however, some individuals, particularly males, may be so mildly affected as to not come to medical attention until adulthood.

Note: It is possible that penetrance in females with germline mutations has not been fully ascertained yet because discovery of the gene and availability of clinical molecular genetic testing are so recent.

Anticipation

Although fathers with focal dermal hypoplasia are typically more mildly affected than their daughters [Burgdorf et al 1981], this discrepancy is attributed to mosaicism in the males rather than anticipation [Wang et al 2007].

When the first affected female in the family has milder manifestations than affected females in subsequent generations [Wechsler et al 1988, Kilmer et al 1993], it is most likely that she has either mosaicism for the *PORCN* mutation or skewing of X-chromosome inactivation, and not true anticipation. Alternative explanations could be reduced reproductive fitness in severely affected females, such that only mildly affected females reproduce.

Nomenclature

Focal dermal hypoplasia is also known by the following eponyms:

- Goltz syndrome
- Goltz-Gorlin syndrome

Note: Gorlin-Goltz syndrome is another name for nevoid basal cell carcinoma syndrome.

Note that not all individuals with the disorder focal dermal hypoplasia have focal areas of skin hypoplasia.

Prevalence

There are no good estimates of the prevalence of focal dermal hypoplasia; it appears to be rare.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Microphthalmia with linear skin defects (MLS). Similar skin and ophthalmologic manifestations may be seen in MLS; however, limb and skeletal malformations are uncommon in MLS. MLS is caused by deletions and point mutations of the *HCCS* gene [Wimplinger et al 2006]; thus, MLS and focal dermal hypoplasia are not allelic, as was previously proposed [Van den Veyver 2002].

Incontinentia pigmenti (IP) is a disorder that affects the skin, hair, teeth, nails, eyes, and central nervous system. Characteristic skin lesions evolve through four stages: (I) blistering (birth to age ~4 months); (II) a wart-like rash (for several months); (III) swirling macular hyperpigmentation (age ~6 months into adulthood); (IV) linear hypopigmentation. Alopecia, hypodontia, abnormal tooth shape, and dystrophic nails are observed. Neovascularization of the retina, present in some individuals, predisposes to retinal detachment. Neurologic findings including cognitive delays/mental retardation are occasionally seen. *IKBKG(NEMO*) is the only gene known to be associated with IP. IP is inherited in an X-linked manner and is lethal in many males.

The combination of **focal dermal hypoplasia**, **morning glory anomaly**, and **polymicrogyria** has been observed in one individual [Giampietro et al 2004]; the eye abnormalities and polymicrogyria make this disorder seem distinct from focal dermal hypoplasia (i.e., Goltz syndrome), the subject of this *GeneReview*.

Oculocerebrocutaneous syndrome predominantly affects males and can be distinguished from focal dermal hypoplasia by the former having characteristic brain malformations, including frontal polymicrogyria, periventricular nodular heterotopia, and agenesis of the corpus callosum [Moog et al 2005].

Rothmund-Thomson syndrome (RTS) is characterized by poikiloderma, sparse hair, eyelashes, and/or eyebrows/lashes, small stature, skeletal and dental abnormalities, cataracts, and an increased risk for cancer, especially osteosarcoma. The skin is typically normal at birth;

the rash of RTS develops between ages three and six months as erythema, swelling, and blistering on the face and subsequently spreads to the buttocks and extremities. The rash evolves over months to years into the chronic pattern of reticulated hypo- and hyperpigmentation, punctate atrophy, and telangiectases, collectively known as poikiloderma. Hyperkeratotic lesions occur in about one-third of individuals. Skeletal abnormalities include dysplasias, absent or malformed bones (such as absent radii), osteopenia, and delayed bone formation. *RECQL4* is the only gene associated with Rothmund-Thomson syndrome to date. Inheritance is autosomal recessive.

Papillomas of the genital and anal region are common and should not be confused with genital warts.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with focal dermal hypoplasia, the following evaluations are recommended:

- Chest x-ray to evaluate for costovertebral defects and evidence of diaphragmatic hernia
- Eye examination to evaluate for colobomas
- Consideration of abdominal MRI to evaluate for diaphragmatic hernia
- Renal ultrasound examination to evaluate for structural anomalies of the kidneys and urinary collecting system
- Hearing evaluation

Treatment of Manifestations

Skin. For individuals with significant areas of dermal aplasia, regular care with a dermatologist and use of occlusive dressings and antibiotic creams may help prevent secondary infections as erosive lesions may be painful, pruritic, and therefore prone to infection. Some individuals report that lotion is helpful in managing pruritic erosions. Pulsed dye laser therapy has been successful in managing painful, pruritic areas [Alster & Wilson 1995].

Verrucoid papillomas can cause significant morbidity. Large papillomas of the larynx can obstruct swallowing and cause severe GER. Affected individuals should be asked frequently about swallowing problems and, when present, should be referred to an otolaryngologist for evaluation and management with surgical or laser therapy.

An individual with refractory exophytic granulation tissue received significant benefit from a combination of curettage and photodynamic therapy [Mallipeddi et al 2006].

Skeletal system. Impaired functionality associated with syndactyly, oligodactyly, and split-hand/foot malformation may improve with occupational therapy, assistive devices, or surgical intervention.

Camptodactyly often improves with physical and occupational therapy.

Reduction defects of the long bones, such as transverse deficiency of distal radius/ulna or tibia/fibula, may be managed with prostheses as appropriate.

Individuals with scoliosis secondary to costovertebral defects should be referred to an orthopedist when other medical providers are unfamiliar with guidelines for routine monitoring and management.

Management of pain related to diastasis pubis with anti-inflammatory medications and/or physical therapy usually resolves the pain. Individuals with pain refractory to these interventions should consult an orthopedist.

Dental. Abnormalities in the structure and number of teeth may cause dental malocclusion and dissatisfaction with the appearance of the teeth. Orthodontic care may be indicated when dental malocclusion is present. Composite veneers and other aesthetic procedures may be used to improve the appearance of abnormal teeth [Tejani et al 2005].

Other

Consultation with:

- An otolaryngologist prior to general anesthesia for evaluation for papillomas of the tonsils or pharynx that would complicate endotracheal intubation

  Note: These lesions may change significantly over time, so the evaluation should be within a few months of the procedure. The papillomas may be friable and prone to bleeding; when papillomas are present the airway must be handled as gently as possible, which may include fiberoptic bronchoscopy for intubation rather than direct laryngoscopy [Rhee et al 2006].
- A pediatric surgeon for the treatment of diaphragmatic hernia and abdominal wall defects
- A urologist or nephrologist for treatment of structural malformations of the kidneys and urinary collecting system

Prevention of Secondary Complications

In individuals with structural renal malformations, standard measures are used to reduce risk for urinary tract infections.

Regular care of a dentist and promotion of good oral hygiene, diet counseling, and consideration of fissure sealants are important to minimize the risk of dental caries [Tejani et al 2005].

Surveillance

The following should be considered as part of routine medical care for individuals with focal dermal hypoplasia:

- Routine follow-up with a dermatologist to anticipate and manage common skin problems
- Preoperative evaluation by an otolaryngologist for hypopharyngeal and tonsillar papillomas
- Questioning about gastroesophageal reflux and swallowing difficulties at routine health visits, and, when present, referral to an otolaryngologist for evaluation of possible verrucoid papillomas and management with surgical or laser therapy as needed
- Routine physical examinations and/or spine radiographs to evaluate for scoliosis, particularly in individuals with costovertebral segmentation abnormalities

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Focal dermal hypoplasia is inherited in an X-linked dominant manner.

Females account for 90% of individuals with focal dermal hypoplasia; they who may have heterozygous or mosaic mutations in *PORCN*. Ten percent of individuals with focal dermal hypoplasia are males; all live-born affected males who have had molecular testing are mosaic for mutations in *PORCN* [Wang et al 2007]. It is presumed that non-mosaic, hemizygous males are not viable.

Risk to Family Members

Parents of a female proband

- Most females with focal dermal hypoplasia have a new gene mutation.
- Approximately 5% of affected females have inherited the mutation from a parent, usually the mother.
- An affected female has been reported to have inherited the mutation from her father, who is mosaic for a *PORCN* mutation [Wang et al 2007].
- Clinical evaluation of both parents of an affected female is warranted. If the disease-causing mutation has been identified in the proband, molecular genetic testing of the parent who has manifestations of focal dermal hypoplasia is appropriate. If neither parent has disease manifestations, molecular genetic testing of both parents should be considered because of the possibility of low-level mosaicism in the father or mother or non-penetrance of the phenotype in the mother.

- Evaluation of the mother may determine that she is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Parents of a male proband

- Live-born affected males are rare and are the result of somatic mosaicism for a new, presumably post-zygotic, mutation.
- Affected males who do not survive pregnancy may have inherited the *PORCN* mutation from their mothers or may have a *de novo*, non-mosaic mutation.
- The father of an affected male will not have the disease nor will he be a carrier of the mutation.

Sibs of a female proband

- The risk to sibs of a female proband depends on the genetic status of the parents.
- When the mother of an affected female is also affected and/or has the disease-causing mutation, the risk to sibs of inheriting the mutant allele at conception is 50%; however, most male conceptuses with the mutant allele are presumed to be spontaneously aborted. Thus, at delivery, the expected sex ratio of offspring is 33% unaffected females, 33% affected females, and 33% unaffected males.
- When the father of an affected female has the disease-causing mutation, the risk to female sibs of inheriting the mutant allele at conception is as high as 100% depending on the level of mosaicism in the father's germline. Female offspring of affected fathers who have been reported are more severely affected than their fathers. Male sibs are not at risk of inheriting the mutation from their father.

Sibs of a male proband. Because evidence from both molecular studies and clinical reports indicates that all live-born males are mosaic for post-zygotic mutations, the risk to the sib of an affected male is similar to the population risk for this disorder.

Offspring of a female proband

- The risk to the offspring of females with focal dermal hypoplasia must take into consideration the presumed lethality to males during gestation.
- At conception, the risk that the mutant *PORCN* allele will be transmitted is 50%; however, most male conceptuses with the mutant *PORCN* allele are presumed to be spontaneously aborted. Thus, at delivery the expected sex ratio of offspring is 33% unaffected females, 33% affected females, and 33% unaffected males.
- If the affected female has a mosaic mutation, the risk to her offspring is as high as 50%, depending on the level of mosaicism in her germline.

Offspring of a male proband

- Males with focal dermal hypoplasia have somatic mosaicism for mutations in *PORCN*. The risk to an affected male of having an affected daughter is as high as 100% depending on the level of mosaicism in his germline.
- Males do not transmit their X chromosome to their sons and thus their sons are not at risk of inheriting a *PORCN* mutation.

Other family members of a proband. If the mother of the proband also has a disease-causing mutation, her female family members may also be at risk of having the disease-causing

mutation (asymptomatic or symptomatic) and her father may be at risk of having the disease-causing mutation (asymptomatic or symptomatic).

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young women who are affected.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis at 16-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Focal Dermal Hypoplasia

Gene Symbol	Chromosomal Locus	Protein Name
PORCN	Xp11.23	Probable protein-cysteine N-palmitoyltransferase porcupine

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Focal Dermal Hypoplasia

300651	PORCUPINE, DROSOPHILA, HOMOLOG OF; PORCN
305600	FOCAL DERMAL HYPOPLASIA; DHOF

Table C. Genomic Databases for Focal Dermal Hypoplasia

Gene Symbol	Entrez Gene
PORCN	64840 (MIM No. 300651)

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *PORCN* gene has 15 exons, 14 of which are coding exons. It undergoes alternative splicing, resulting in five transcript variants.

Pathologic allelic variants: Disease-causing mutations include nonsense, frameshift, and missense mutations as well as genomic deletions that delete the entire *PORCN* locus. The deletions also delete a variable number of flanking genes [Grzeschik et al 2007, Wang et al 2007].

Normal gene product:*PORCN* encodes the human homolog of *Drosophila* porcupine [Caricasole et al 2002]. The gene product, human porcupine homolog, has five isoforms that result from alternative splicing and is expressed in a wide variety of tissues. Most information about its function is derived from studies of its highly conserved mouse and *Drosophila* homologs, where it has been shown to be required for secretion of certain WNT proteins from WNT-producing cells. WNTs are important morphogens that are secreted from producing cells and interact with specialized receptors and co-receptors (FZD/LRP5 or 6) on target cells. This activates the canonical WNT pathway, resulting in intracellular stabilization and translocation into the nucleus of β-catenin, where it activates specific target genes that are important for normal development [Clevers 2006]. Wnt-3a is retained in the endoplasmic reticulum of cultured cells when *Porcn* is inactivated [Takada et al 2006]. Wnt signaling is required for induction, proliferation, morphogenesis, and maintenance of most organs. RNA in situ studies of mouse embryos at embryonic day 14.5 have demonstrated *Porcn* expression in the skin, retina, middle ear, tooth bud, long bones, ribs, vertebrae, bones of the paws, cranium, and frontal lobe of the brain [Wang et al 2007].

Abnormal gene product: Focal dermal hypoplasia is caused by loss-of-function mutations and deletions of *PORCN*. It is currently unknown how the mutations in *PORCN* identified in humans affect porcupine function and canonical WNT signaling. However, loss of function of its orthologs in mouse cells and *Drosophila* results in failure of WNT proteins to be secreted from the endoplasmic reticulum in WNT-producing cells, with defective downstream WNT signaling [Tanaka et al 2000, Takada et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Ectodermal Dysplasia Society
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Phone: 618-566-2020
Fax: 618-566-4718

Email: info@nfed.org
www.nfed.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

http://www.bcm.edu/genetics/facultyaz/sutton.html

http://www.bcm.edu/genetics/facultyaz/vandenveyver.html

Revision History

- 15 May 2008 (me) Initial posting
- 6 February 2008 (vrs) Original submission

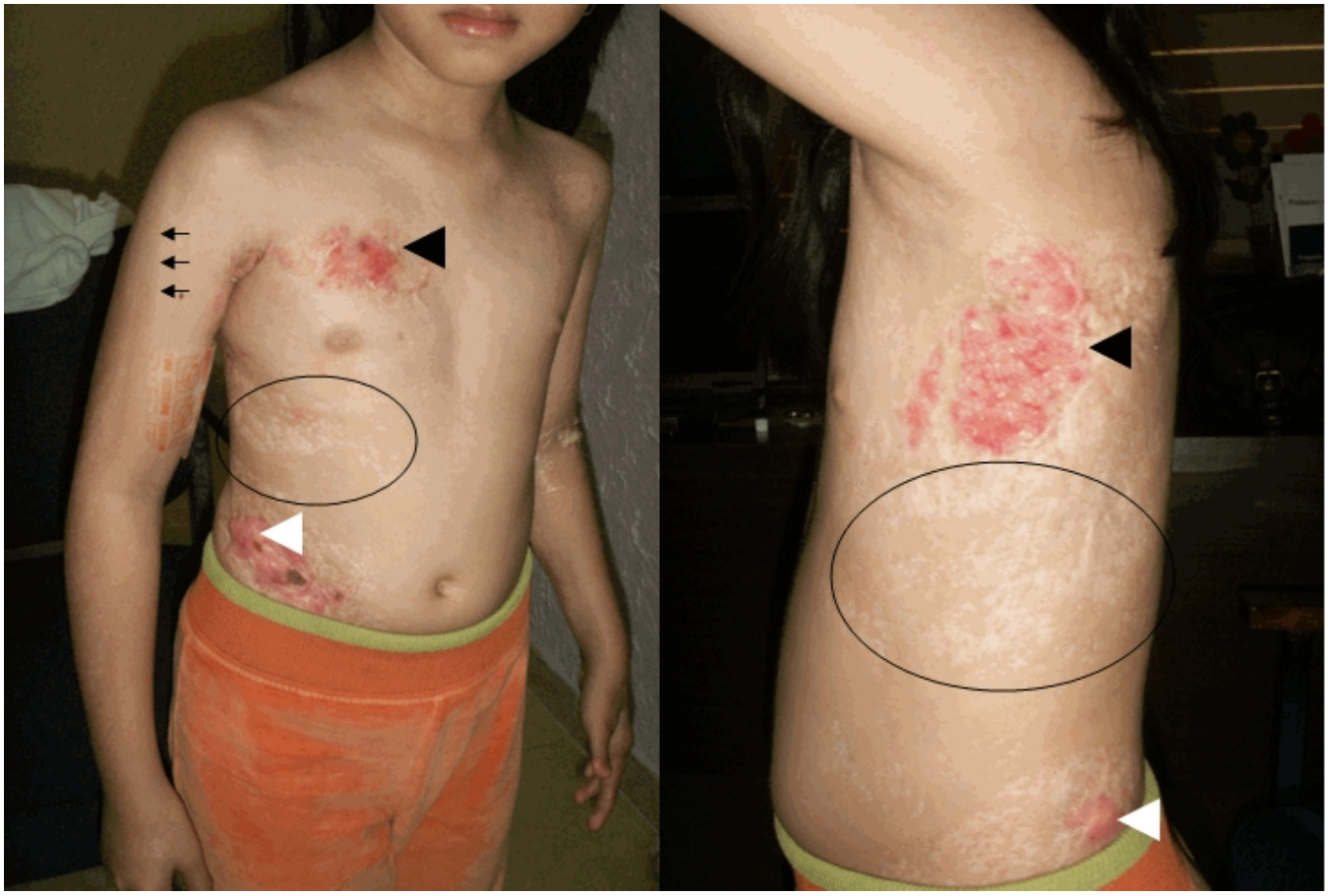

Figure 1. Skin manifestations include yellowish-pink areas representing fat herniation (white arrowheads), aplasia (black arrowheads), hyperpigmentation following lines of Blaschko (black arrows indicating the border) and hypopigmented areas of poikiloderma (circled regions).

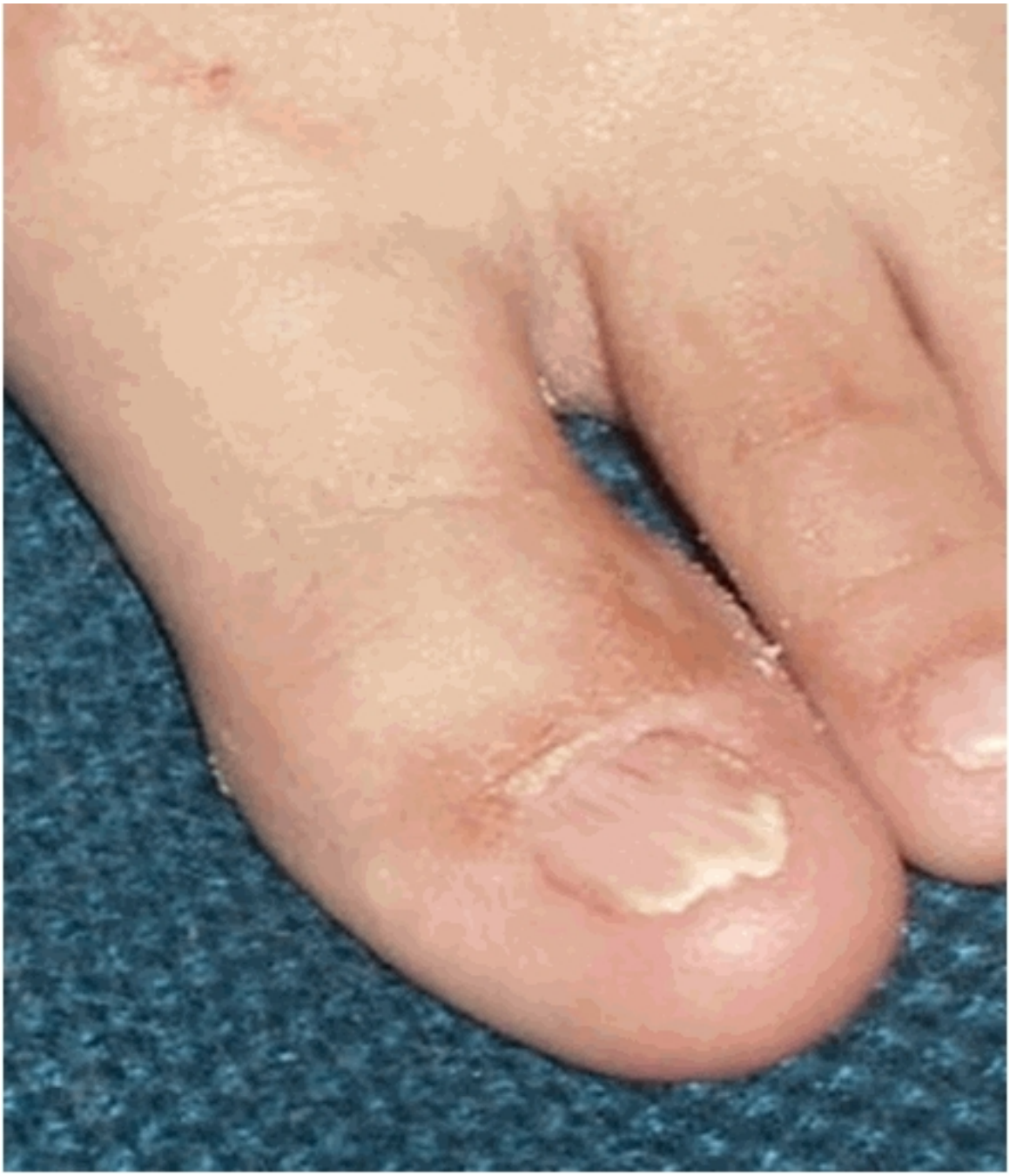

Figure 2. Left great toe showing underdevelopment and ridging of the nail.

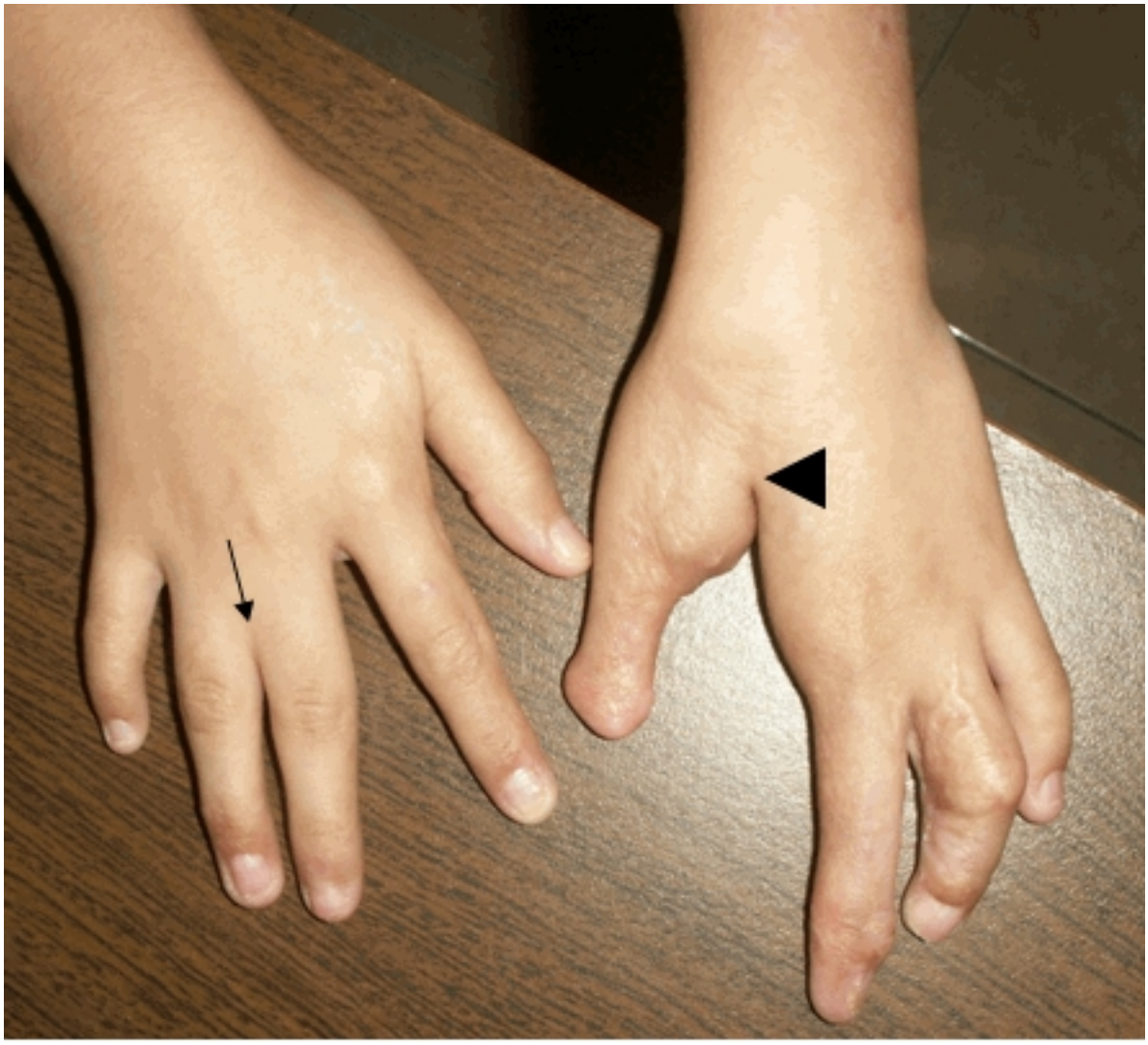

Figure 3. Hands showing syndactyly (black arrow) and split-hand malformation (black arrowhead) with only four digits (oligodactyly) on the left hand; the appearance of the left hand has been somewhat modified by partial surgical repair.

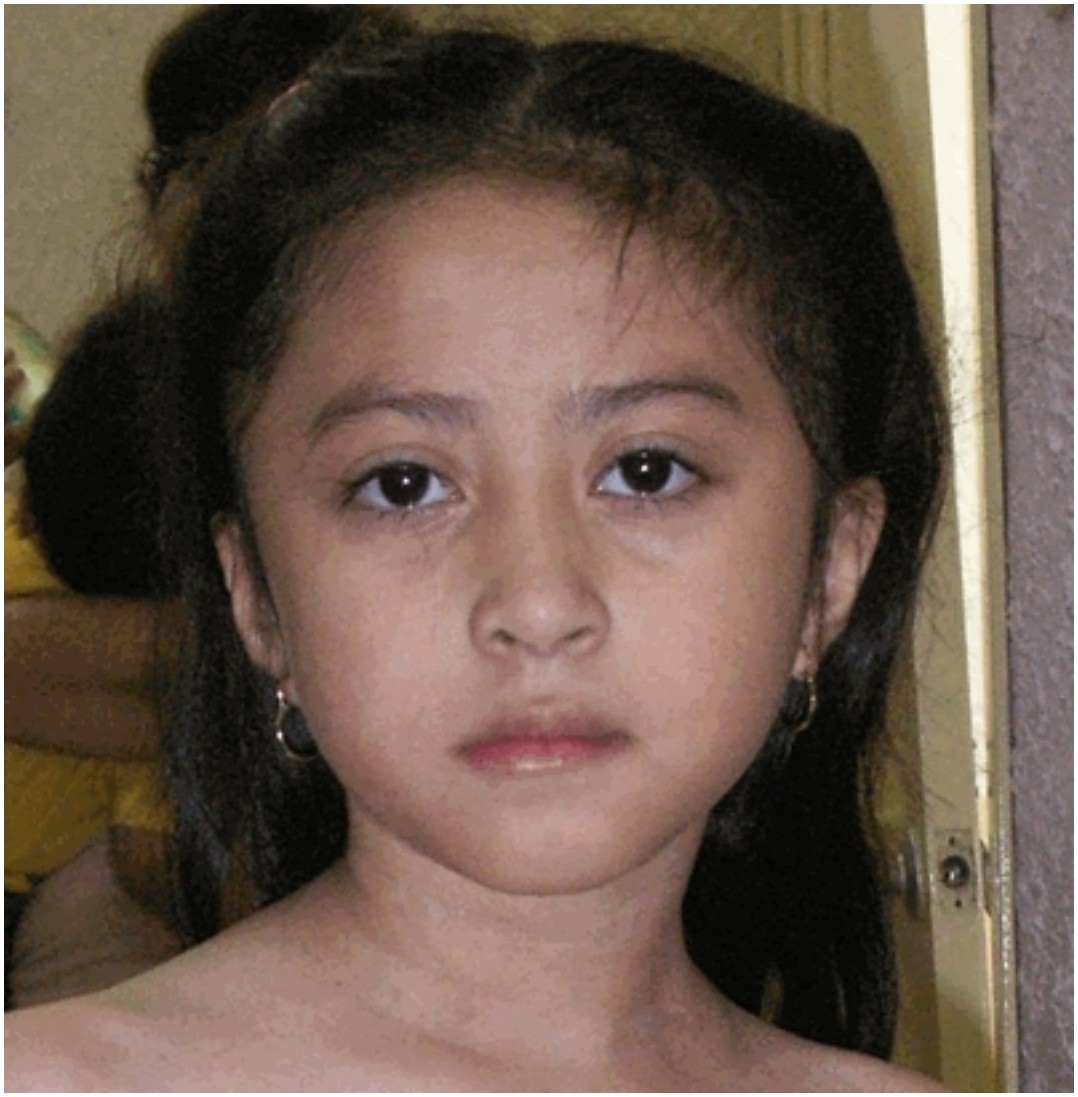

Figure 4. Note facial features of pointed chin and small right ear.