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Focal Dermal Hypoplasia

Synonyms: Goltz Syndrome, Goltz-Gorlin Syndrome

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Summary

Clinical 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

Focal dermal hypoplasia can be diagnosed based on clinical findings in individuals with classic ectodermal findings and characteristic limb malformations. Molecular genetic testing may be useful to confirm the diagnosis in these individuals and is used to establish the diagnosis in individuals in whom the clinical findings are inconclusive.

Management

Treatment of manifestations: Care by a dermatologist for painful and pruritic erosive lesions that are prone to infection; referral to an otolaryngologist or gastroenterologist for evaluation and management of large papillomas of the larynx and/or trachea or esophagus causing gastroesophageal disease (GERD); referral to a physical/occupational therapist and hand surgeon for management of hand and foot malformations; standard

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protocols for management of structural abnormalities of the eyes and kidneys and diaphragmatic hernia and abdominal wall defects.

Prevention of secondary complications: Preoperative evaluation by an otolaryngologist for hypopharyngeal and/or tonsillar papillomas.

Surveillance: Routine follow up with a dermatologist; routine evaluations for scoliosis, particularly in individuals with costovertebral segmentation abnormalities; routine monitoring of growth and body composition to determine need for nutritional intervention; regular eye examinations; routine screening for cognitive, emotional, behavioral, and adaptive issues.

Genetic counseling

Focal dermal hypoplasia is inherited in an X-linked manner. Females (90% of affected individuals) are heterozygous or mosaic for a *PORCN* pathogenic variant; live-born affected males (10% of affected individuals) are mosaic for a *de novo PORCN* pathogenic variant. It is presumed that non-mosaic hemizygous males are not viable. Approximately 95% of females with focal dermal hypoplasia have a *de novo* pathogenic variant; ~5% inherited the pathogenic variant from a parent. The risk that the *PORCN* pathogenic variant will be transmitted by an affected heterozygous female is 50%; however, because most male conceptuses with a *PORCN* pathogenic variant are presumed to be spontaneously aborted, at delivery the expected sex ratio of offspring is: 33% unaffected females; 33% affected females; 33% unaffected males. If the affected female is mosaic for a *PORCN* pathogenic variant, the risk to her female offspring of inheriting the pathogenic variant depends on the level of mosaicism in her germline and can be as high as 50%. Prenatal diagnosis for pregnancies at increased risk and preimplantation genetic diagnosis are possible if the pathogenic variant in the family has been identified.

Diagnosis

Suggestive Findings

Focal dermal hypoplasia, a multisystem disorder primarily involving the skin, skeletal system, eyes, and face, **should be considered** in an individual with following clinical findings.

Major Findings

Characteristic **ectodermal manifestations** include the following (see Figure 1):

- **Congenital patchy skin aplasia** (95% of individuals) evidenced by 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.
- **Congenital skin hypo- or hyperpigmentation** (90%-100%) often following a Blaschko linear distribution
- **Congenital nodular fat herniation** (60%-70%), evidenced by soft, yellow-pink nodules on the skin (which represent fat nodules in the dermis) that are typically seen on the trunk and extremities
- **Congenital ridged, dysplastic, or hypoplastic nails** (80%-90%)
- **Telangiectasias** (~80%) (may be seen on the face, trunk, and extremities)

Characteristic **limb malformations** [Smith & Hunt 2016] include the following (see Figure 2 and Figure 3):

- **Syndactyly** (70%-90% of individuals) joining or webbing of ≥2 fingers or toes, occurring variably on one or more extremities
- **Ectrodactyly** (75%), a split hand/foot malformation that may occur on one or more extremities
- **Oligodactyly** (20%-40%) – <5 digits on a hand or foot, which may be seen in one or both hands or feet. Central digits are more frequently involved.
- **Transverse limb defect** (15%) – congenital absence of the hand, wrist, forearm, or elbow with no distal remaining portions, including acheiria or hemimelia
- **Long bone reduction defect** (50%-80%) – hypoplasia or shortening of the long bones in one or more extremities

Minor Findings

Additional common features not included in the diagnostic criteria but supportive of the diagnosis include the following.

Ectodermal manifestations [Bree et al 2016, Wright et al 2016]

- Patchy alopecia of the scalp (80% of individuals) or wiry hair (65%)
- Verrucoid papillomas (65%) of the skin and mucous membranes (including in the mouth, nose, larynx, esophagus, vaginal mucosa, and/or rectal mucosa)
- Dental abnormalities including enamel defects / longitudinal grooving (65%), peg teeth (50%), or hypodontia (80%)
- Photosensitivity (40%)
- Pebbled skin texture (58%)
- Hair shaft abnormalities on scanning electron microscopy (80%-90%)

Ocular manifestations [Gisseman & Herce 2016]

- Iris colobomas (50% of individuals)
- Chorioretinal colobomas (60%)
- Microphthalmia (45%) or anophthalmos (5%-10%)
- Cataracts (10%)
- Nystagmus (30%) or strabismus (20%)

Establishing the Diagnosis

Focal dermal hypoplasia can be diagnosed based on clinical findings in individuals with classic ectodermal findings and characteristic limb malformations. Molecular genetic testing may be useful to confirm the diagnosis in these individuals and is used to establish the diagnosis in individuals in whom the clinical findings are inconclusive.

The diagnosis of focal dermal hypoplasia **is established** in a female or male proband with the following clinical and/or molecular genetic findings.

Clinical Findings

Focal dermal hypoplasia can be diagnosed clinically in individuals with three or more characteristic major ectodermal manifestations AND at least one characteristic major limb malformation [Bostwick et al 2016].

Note: (1) Skin manifestations should be congenital in onset to distinguish from a similar skin phenotype seen in Rothmund-Thomson syndrome. (2) Minor findings alone are not sufficient to establish a clinical diagnosis, but when present should increase suspicion for focal dermal hypoplasia.

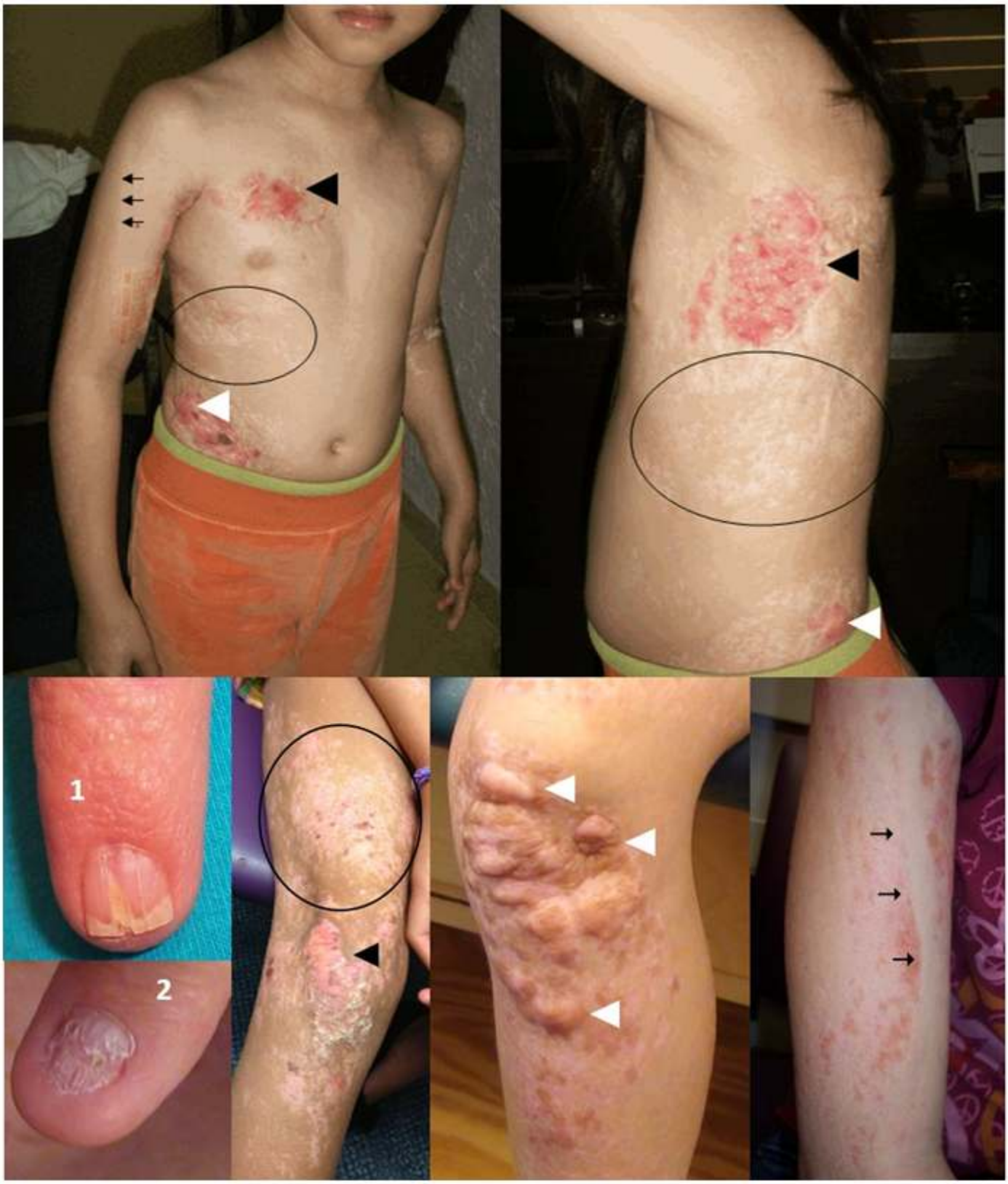

Figure 1. Ectodermal manifestations include yellowish-pink areas representing fat herniation (white arrowheads), patchy aplasia (black arrowheads), hyper-/hypopigmentation following lines of Blaschko (black arrows indicating the border), and hypopigmented areas of poikiloderma (circled regions). The nail phenotype ranges from longitudinal ridging (1) to hypoplastic (2).

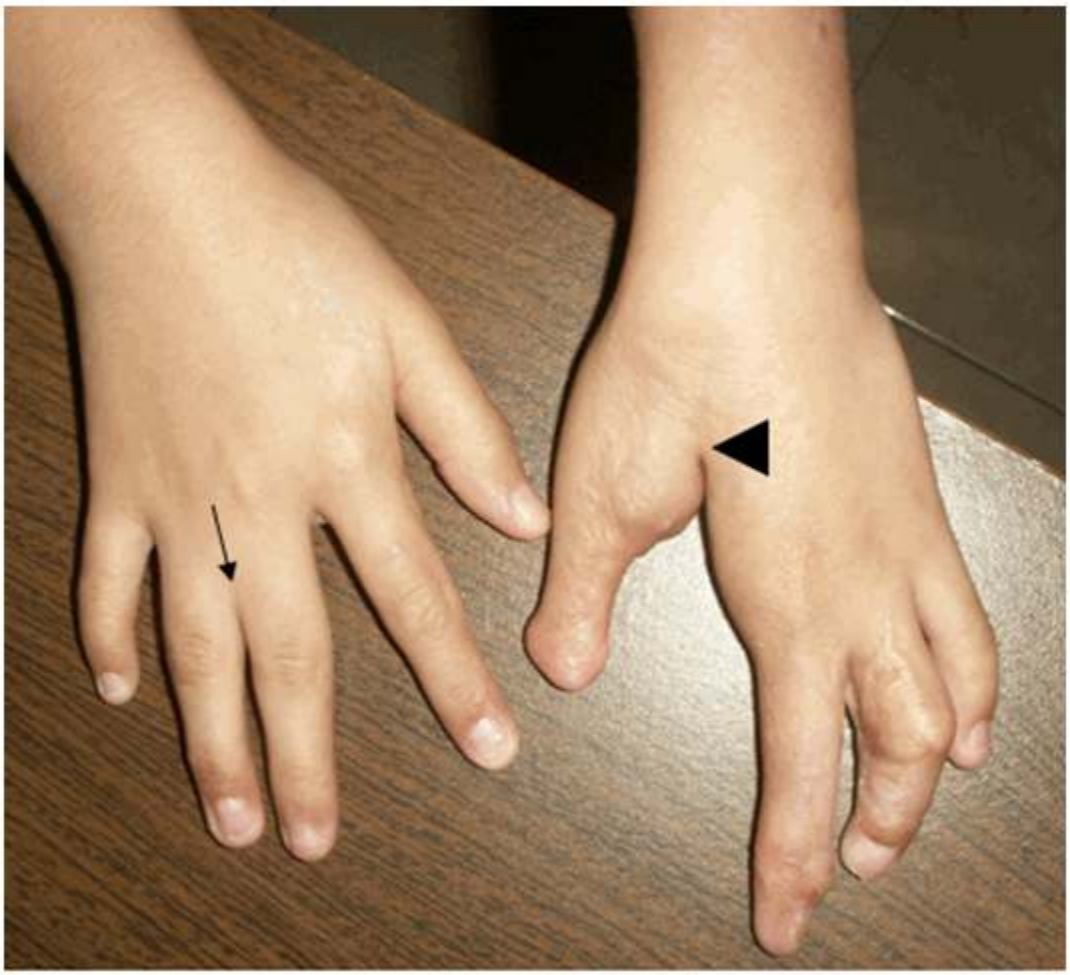

Figure 2. Hands showing syndactyly (black arrow) and split-hand malformation (black arrowhead) with only four digits (oligodactyly) on the left hand. The appearance of the left hand has been somewhat modified by partial surgical repair.

Molecular Genetic Findings

Identification of a germline heterozygous *PORCN* pathogenic variant or deletion in a female or somatic mosaic hemizygous *PORCN* pathogenic variant or deletion in a male (see Table 1) confirms the diagnosis in individuals with characteristic clinical findings and establishes the diagnosis when clinical findings are ambiguous or inconclusive.

Note: Nearly all affected males to date have somatic mosaicism for a hemizygous *PORCN* pathogenic variant [Grzeschik et al 2007, Wang et al 2007, Lombardi et al 2011]; the one notable exception is two brothers who were hemizygous for an inherited novel *PORCN* missense variant that was likely a hypomorphic allele [Brady et al 2015].

Tiered molecular testing approaches can include a combination of **single-gene testing** (sequence analysis and gene-targeted deletion/duplication analysis), **chromosomal microarray analysis (CMA)**, use of a **multigene panel**, and **more comprehensive genomic testing**.

First-tier testing. On a blood sample, perform sequence analysis of *PORCN*. If no pathogenic variant is identified, perform either CMA (if not already performed) to detect large deletions/duplications that include *PORCN* or gene-targeted deletion/duplication analysis of *PORCN* if CMA was normal; note, however, that intragenic deletions detected by this method have been reported rarely (see Table 1).

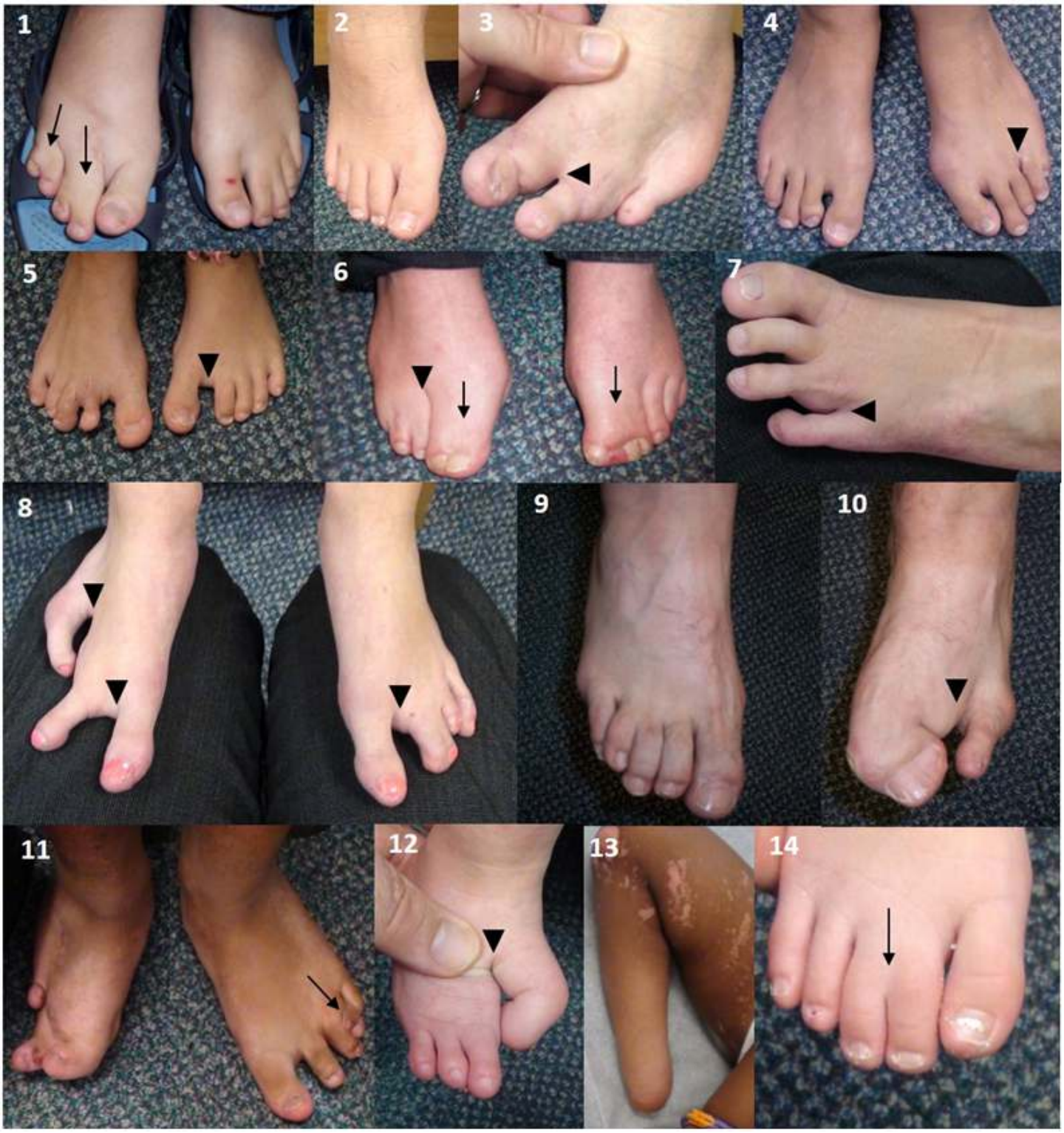

Figure 3. Highly variable limb malformations

Feet showing syndactyly (black arrow), split-hand malformation or ectrodactyly (black arrowhead), oligodactyly (3, 6, 7, 8, 10, 11, 12), and distal transverse limb defect (13)

Adapted from Bostwick et al [2016]

Note: (1) Several females and nearly all males have somatic mosaicism for either a *PORCN* pathogenic variant or *PORCN* deletion; therefore, possible mosaicism must be considered when performing sequence analysis (see

Second-tier testing). (2) A male with a 47,XXY karyotype and a heterozygous *PORCN* pathogenic variant on one of the two X chromosomes has been reported [Alkindi et al 2013].

Second-tier testing. If first-tier testing does not detect a *PORCN* pathogenic variant or deletion, perform sequence analysis and deletion/duplication analysis on saliva or affected tissues (e.g., skin, papillomas, surgical specimens), which increase the sensitivity for detecting somatic mosaicism [Maas et al 2009].

Testing to consider. If first-tier and second-tier testing do not detect a *PORCN* pathogenic variant or deletion, the following may also be considered:

- **A multigene panel** that includes *PORCN* and other genes of interest (see Differential Diagnosis). 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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

Table 1. Molecular Genetic Testing Used in Focal Dermal Hypoplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method [3, 4]
PORCN	Sequence analysis [5, 6]	~91% [7]
	Deletion/duplication analysis [3] (genomic approach)	~9% [7, 8]
	Gene-targeted deletion/duplication analysis [9]	Rare [7, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Estimates based on 170 individual positive test results curated in the PORCN @ LOVD database [Lombardi et al 2011]
4. Approximately 91% of pathogenic variants are detectable by sequence analysis; ~9% of pathogenic variants are large deletions. Males with mosaic pathogenic variants represent ~10% of all described cases with pathogenic variants in PORCN @ LOVD [Bornholdt et al 2009, Froyen et al 2009, Fernandes et al 2010, Lombardi et al 2011].
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
7. Nearly all 46,XY males and some females are mosaic for pathogenic variants in *PORCN*. When using sequence analysis, mosaicism for a pathogenic variant may result in a false negative test result [Grzeschik et al 2007, Wang et al 2007, Bornholdt et al 2009, Maas et al 2009, Fernandes et al 2010, Vreeburg et al 2011, Yoshihashi et al 2011].
8. Reported deletions have ranged from an intragenic deletion (exons 1-4) [Bornholdt et al 2009] to large genomic deletions including *PORCN* and neighboring genes of up to 0.5 Mb [Wang et al 2007, Lombardi et al 2011].
9. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Note that although gene-targeted deletion/duplication assays may detect smaller events than genomic deletion/duplication assays, they may not determine the size of a larger event.

Clinical Characteristics

Clinical Description

Focal dermal hypoplasia is a highly variable multisystem disorder caused by developmental abnormalities in mesodermal and ectodermal structures primarily involving the skin, limbs, eyes, and face. The manifestations vary among affected individuals and many have only a subset of the characteristic features.

Females account for 90% of individuals with focal dermal hypoplasia.

The phenotypes in both males and females are highly variable due to tissue mosaicism: females have random X-chromosome inactivation (functional mosaicism) while males nearly always have postzygotic somatic mosaicism.

Affected Females

Ectodermal manifestations. The most characteristic features of focal dermal hypoplasia are the skin manifestations (Figure 1). The cutaneous findings typically follow the lines of Blaschko and include patchy areas of skin aplasia/hypoplasia, skin hypo- and/or hyper-pigmentation, and nodular fat herniation. The lines of Blaschko represent cell migration pathways that are linear on the limbs and circumferential on the trunk. The lines are classically described as V-shaped overlying the upper spine, S-shaped on the abdomen, and an inverted-U shape from the breast area to the upper arms. These findings are typically evident at birth, but the distribution and severity may change over time. Unilateral involvement has also been reported [Tenkir & Teshome 2010, Maalouf et al 2012, Asano et al 2013].

Other integumentary system abnormalities include wiry hair, sparse hair, patchy alopecia of the scalp, and abnormal nails. The nails can be absent (anonychia), small (micronychia), hypoplastic, or dysplastic, often with longitudinal ridging, splitting, or V-nicking [Bree et al 2016].

Papillomatosis. Papillomas and telangectasias are typically not present at birth but develop with age.

- Verrucoid papillomas are found in the oral mucosa of the mouth, nose, pharynx, larynx, trachea, and esophagus. Large papillomas of the larynx can obstruct breathing during anesthesia or can cause obstructive sleep apnea. Papillomas in the esophagus or larynx can also cause or contribute to severe GERD.
- The vaginal or rectal mucosa are also common sites for papillomas, where they can be confused with genital warts.

Dental abnormalities and eye findings, both of which result from abnormalities in ectodermal appendage development, are described separately below.

Limb and skeletal manifestations. Most individuals with focal dermal hypoplasia have limb malformations noted at birth, including syndactyly, oligodactyly, and split-hand/foot malformation or ectrodactyly (Figure 2 and Figure 3) [Gorlin et al 1963, Goltz et al 1970]. These malformations, which do not change over time, may impair function.

Additionally, reduction defects of the long bones ranging from leg length discrepancies to transverse defects of the distal radius/ulna or tibia/fibula are commonly seen.

Less common limb malformations that may be present at birth and impair function include camptodactyly (contraction deformities of the digits) and brachydactyly (shortening of the digits).

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. Kyphosis or kyphoscoliosis is seen in approximately 10% of affected individuals [Smith & Hunt 2016]. 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.

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.

Osteopathia striata, a striated appearance of the bones evident on plain x-rays, is common and may be seen in childhood, adolescence, and adulthood. It is currently unclear if individuals with this finding are at increased risk for general osteoporosis. Of note, a spontaneous patella fracture related to osteoporosis in a patient with FDH has been reported [Altschuler et al 2012].

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 20/20 to no light perception. Reported eye abnormalities include anophthalmia/microphthalmia; microcornea; iris, chorioretinal and eyelid colobomas; lacrimal duct abnormalities; and cataracts (cortical and subcapsular) [Gorlin et al 1963, Goltz et al 1970].

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 (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].

Oral and dental findings. Oral manifestations are seen in more than half of affected individuals and include both soft tissue and hard tissue abnormalities.

Enamel hypoplasia that predisposes to dental caries is the most common problem. Other findings include: hypodontia, oligodontia, supernumerary teeth, and dental crowding leading to malocclusion of both primary and secondary dentition; vertical grooving of the teeth; microdontia (small teeth); taurodontia (prism-shaped molars); fused teeth; and abnormal root morphology [Balmer et al 2004, Tejani et al 2005, Murakami et al 2011]. Affected individuals may also have problems with the eruption and position of teeth. Natal teeth were described in one affected individual [Dias et al 2010].

Soft tissue abnormalities include generalized gingivitis and intra-oral lipomas and papillomas.

Gastrointestinal and nutrition. Problems include poor weight gain (77% of individuals), short stature (65%), oral motor dysfunction (41%), gastroesophageal reflux (24%), gastroparesis (35%), and constipation (35%) [Motil et al 2016]. Food allergies – primarily to milk, soy, and shellfish – are present in 12% of affected individuals.

Other developmental abnormalities of the digestive system are rare but may have severe consequences; they include abdominal wall defects and diaphragmatic hernia (see Congenital Diaphragmatic Hernia Overview).

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

Renal and urogenital. Genital labial hypoplasia is present in most females [Adeyemi-Fowode et al 2016]. Occasional affected individuals with müllerian anomalies, including bicornuate uterus, have been described [Reddy & Laufer 2009, Lopez-Porras et al 2011].

Renal structural abnormalities are uncommon, but previous case reports include unilateral absent kidney, hypoplastic kidney, fused/horseshoe kidney, or cystic renal dysplasia. If present, these abnormalities may lead to recurrent urinary tract infections and urinary reflux [Suskan et al 1990].

Cognitive and psychological. Development and intellectual ability is normal in most individuals. Intellectual impairment (15%-20% of individuals), behavioral problems (~20%), emotional lability (40%-50%), and withdrawn behavior (65%) have been reported [Deidrick et al 2016]. In those with emotional, behavioral, adaptive, and intellectual impairment, the spectrum of severity varies widely.

Structural brain abnormalities and spina bifida [Goltz et al 1970, Almeida et al 1988] have been reported but are uncommon.

Epilepsy has been reported [Kanemura et al 2011].

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

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* pathogenic variant or skewing of X-chromosome inactivation. Alternative explanations could be reduced reproductive fitness in severely affected females, such that only mildly affected females reproduce.

Affected Males

Because relatively few affected males have been reported, no comprehensive data for a "typical" male phenotype exist.

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, Bornholdt et al 2009, Maas et al 2009, Lombardi et al 2011, Lasocki et al 2011, Vreeburg et al 2011, Yoshihashi et al 2011].

Affected males have somatic mosaicism for a *PORCN* pathogenic variant and are generally more mildly affected than females [Grzeschik et al 2007, Wang et al 2007, Lombardi et al 2011]. Of note, fathers with focal dermal hypoplasia are typically more mildly affected than their daughters [Burgdorf et al 1981], a discrepancy attributed to mosaicism in the males.

Severe Presentations

Various phenotypes have been previously described as separate syndromes or potentially allelic conditions, but are now recognized to be within the spectrum of focal dermal hypoplasia.

Angioma serpiginosum was initially hypothesized to be allelic to focal dermal hypoplasia [Blinkenberg et al 2007]. A deletion of *PORCN* was subsequently reported in one affected individual [Houge et al 2008], but this was later disputed and proposed to be a case of FDH instead of a case of angioma serpiginosum [Happle 2009].

According to Van Allen & Myhre [1991], Van Allen-Myhre syndrome was either a severe form of focal dermal hypoplasia or allelic to focal dermal hypoplasia. This has been confirmed in a report in which an individual with Van Allen-Myhre syndrome [Hancock et al 2002] was found to have a pathogenic variant in *PORCN* [personal observation; case reported by Wang et al 2007].

FDH with abdominal wall closure defects that are in the spectrum of pentalogy of Cantrell or limb-body wall complex anomaly have been reported [Hancock et al 2002, Maas et al 2009, Scott et al 2009, Smigiel et al 2011]. In some of these affected individuals, *PORCN* pathogenic variants have been detected [Maas et al 2009, Lombardi et al 2011, Smigiel et al 2011]. Whether pathogenic variants in *PORCN* can cause isolated forms of these conditions has not been established.

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].

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

- From biopsies from Blaschkoid streaks, findings of increased papillary dermal blood vessels, decreased thickness of the dermis, and adipocytes high in the dermis strongly point to the diagnosis of focal dermal hypoplasia [Ko et al 2016].

Genotype-Phenotype Correlations

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

Available data suggest that the level of X-chromosome inactivation correlates with severity of the phenotype in some (familial) cases [Grzeschik et al 2007, Wang et al 2007].

Note: All females with deletions in *PORCN* have extremely skewed X-chromosome inactivation, whereas females with a single-nucleotide variant can have random or skewed X-chromosome inactivation [Grzeschik et al 2007, Wang et al 2007, Lombardi et al 2011].

Nearly all affected males to date have somatic mosaicism for a *PORCN* pathogenic variant, with males being generally more mildly affected than females; however, some severely affected males have been reported [Maas et al 2009, Bornholdt et al 2009, Lombardi et al 2011]. One notable exception is two brothers who were hemizygous for an inherited novel *PORCN* missense variant thought to contribute to syndromic microphthalmia [Brady et al 2015]. The phenotypic severity in female relatives harboring the same variant ranged from mild to unaffected, suggesting a probable hypomorphic allele.

Penetrance

Focal dermal hypoplasia appears to be highly penetrant in females, but the phenotypic severity can occasionally be mitigated by skewed X-chromosome inactivation.

Males are nearly always mosaic for a hemizygous somatic *PORCN* pathogenic variant and can be so mildly affected as to not come to medical attention until adulthood.

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

Focal dermal hypoplasia is an uncommon disorder with about 300 reported affected individuals worldwide [Goltz 1992, Tadini et al 2015]. The exact prevalence is unknown.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *PORCN*.

Differential Diagnosis

Microphthalmia with linear skin defects (MLS) can have skin and ophthalmologic manifestations similar to FDH; however, limb and skeletal malformations are uncommon in MLS. MLS is caused by deletions and variants in *HCCS* [Wimplinger et al 2006]. MLS is inherited in an X-linked manner and mainly affects females as it is usually lethal in males.

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 / intellectual disability 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.

***TP63*-related disorders** are characterized by a varying combinations of limb malformations (split-hand/foot malformation, syndactyly) and ectodermal findings (skin erosions, hypoplastic breast tissue, hypopigmentation of the skin, nail dysplasia, alopecia, dental abnormalities). However, the skin manifestations are typically not in a Blaschko distribution and ocular colobomas and microphthalmia are rare. These disorders are caused by heterozygous pathogenic variants in *TP63*, affecting both males and females.

Oculocerebrocutaneous syndrome (OMIM 164180) is characterized by microphthalmia/anophthalmia, orbital cysts, linear skin pigmentation, and dermal hypoplasia. The condition predominantly affects males and can be distinguished from focal dermal hypoplasia by presence (in the former) of characteristic brain malformations

including frontal polymicrogyria, periventricular nodular heterotopia, and agenesis of the corpus callosum [Moog et al 2005]. No gene in which mutation is causative has been identified.

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 (e.g., absent radii), osteopenia, and delayed bone formation. RTS is caused by biallelic pathogenic variants in *RECQL4* and is inherited in an autosomal recessive manner.

Other. 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 and needs in an individual diagnosed with focal dermal hypoplasia, the following evaluations are recommended.

- **Ectodermal manifestations.** Evaluation by a dermatologist for identification of dermal aplasia or erosive skin that may benefit from treatment with dressings or lotion
- **Papillomatosis**
  - Evaluation by an otolaryngologist for evidence of laryngeal or peri-tonsillar verrucoid papillomas, which can cause obstructive sleep apnea
  - Sleep study to evaluate for obstructive sleep apnea (often due to airway papillomas)
- **Limb and skeletal manifestations.** Chest x-ray to evaluate for costovertebral defects and evidence of diaphragmatic hernia
- **Eye findings.** Eye examination to evaluate for iris colobomas, chorioretinal colobomas, nystagmus, strabismus, or cataracts
- **Oral and dental findings**
  - Evaluation by a cleft palate team if relevant
  - Examination by a dentist beginning with the first teeth around age one year
- **Gastrointestinal and nutrition**
  - Consideration of abdominal ultrasound examination to evaluate for diaphragmatic hernia
  - Evaluation by a gastroenterologist if gastroesophageal reflux disease (GERD) is an issue
- **Renal and urogenital**
  - Renal ultrasound examination to evaluate for structural anomalies of the kidneys and urinary collecting system
  - Evaluation by a pediatric gynecologist prior to puberty. Imaging studies of the reproductive tract should be considered as anomalies can affect fertility.
- **Cognitive and psychological.** Hearing evaluation
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Skin. For individuals with significant areas of dermal aplasia, regular care by a dermatologist and use of occlusive dressings and antibiotic creams may help prevent secondary infections as erosive lesions may be painful and pruritic, and therefore prone to infection. Some individuals report that lotion is helpful in managing

pruritic erosions. Pulsed dye laser or other photodynamic therapy has been successful in managing excessive granulation tissue [Alster & Wilson 1995, Liu et al 2012].

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

An adult individual with multiple cutaneous basal cell carcinomas has been reported. Whether this is more prevalent in FDH is currently unknown, but heightened surveillance and appropriate treatment for such lesions may be indicated [Patrizi et al 2012].

Papillomatosis. Verrucoid papillomas can cause significant morbidity, including breathing problems (which could reflect the presence of laryngeal and/or tracheal papillomas) and GERD symptomatology (which could reflect the presence of esophageal papillomas). When possible, individuals should be referred to an otolaryngologist or gastroenterologist depending on the anatomic location of the papillomas.

Symptomatic papillomas of the esophagus can be removed endoscopically [Kashyap et al 2011] or with balloon-assisted radiofrequency ablation [Bertani et al 2014]. Airway (hypopharyngeal, tonsillar, and tracheal) papillomas can be managed with surgery or laser therapy.

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

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

Camptodactyly often improves with physical and occupational therapy.

Individuals with scoliosis secondary to costovertebral defects should be referred to an orthopedist 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.

Eye. Colobomas of the eyelid may be repaired by an oculoplastic surgeon.

Iris colobomas can be aesthetically treated with colored contact lenses to give the appearance of a round pupil.

The photophobia that often accompanies iris colobomas can be reduced by use of tinted glasses.

Because retinal detachment leading to blindness is a potential complication of retinal coloboma, any acute changes in vision should be evaluated urgently by an ophthalmologist.

In patients with microphthalmia, an ocularist using prosthetic intervention can work to expand the palpebral fissures. Additional surgical corrections can be discussed with an oculoplastic surgeon.

Children with reduced vision may benefit from visual aids or other visual resources as part of an early intervention program to increase visual-spatial development.

Dental. 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, Murakami et al 2011].

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, Murakami et al 2011].

Other. Consultation with:

- 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 and their sequelae. In individuals with structural renal malformations, standard measures are used to reduce risk for urinary tract infections.
- A developmental pediatrician for evaluation and management of behavioral problems, emotional lability, or withdrawn behaviors. Those with intellectual impairment or developmental delay should receive early intervention in occupational, speech, and physical therapies.

Prevention of Secondary Complications

Preoperative evaluation by an otolaryngologist for hypopharyngeal and tonsillar papillomas [Rhee et al 2006] is indicated prior to general anesthesia. Any papillomas that would complicate endotracheal intubation should be surgically removed or communicated to the anesthesiologist prior to the procedure.

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].

Surveillance

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

- **Skin.** Routine follow-up with a dermatologist to anticipate and manage common skin problems
- **Papillomatosis**
  - Monitoring for symptoms of gastroesophageal reflux disease and swallowing difficulties at routine health visits. When present, refer to an otolaryngologist for evaluation of possible verrucoid papillomas and management with surgical or laser therapy as needed.
  - Routine monitoring for symptoms of obstructive sleep apnea (snoring, gasping, breathing pauses). If present, a sleep study should be performed [Bostwick et al 2016].
- **Skeletal.** Routine physical examinations and/or spine radiographs to evaluate for scoliosis, particularly in individuals with costovertebral segmentation abnormalities
- **Dental.** Regular examinations
- **Other**
  - Routine monitoring of growth and body composition to determine if early nutritional intervention is needed [Motil et al 2016]
  - Regular eye examinations to monitor for changes in visual acuity and risks for retinal detachment in individuals with retinal colobomas. Any acute changes in vision should be considered a medical emergency as retinal detachment can lead to total blindness.
  - Routine screening of cognitive, emotional, behavioral, and adaptive ability, with appropriate referrals to therapeutic interventions as indicated [Deidrick et al 2016]

Agents/Circumstances to Avoid

Because some individuals with severe skin manifestations may have hypohidrosis (and thus be at increased risk for heat intolerance), care should be taken to prevent exposure to extreme heat.

Evaluation of Relatives at Risk

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

Pregnancy Management

For affected women, management of pregnancy should be guided by standard obstetric principles taking into account potential complications of FDH. Skeletal abnormalities including scoliosis or diastasis pubis may be present in some affected women, and may affect delivery management. Women with significant scoliosis will benefit from evaluation of respiratory status and feasibility of epidural analgesia. Obstetricians should be aware that verrucous papillomas in genital areas in women with FDH are unlikely to be viral in origin and thus, there is no risk for transmission to the newborn during vaginal delivery.

Therapies Under Investigation

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. —ED.

Mode of Inheritance

Focal dermal hypoplasia (FDH) is inherited in an X-linked manner.

Females account for 90% of individuals with FDH; they may have heterozygous or mosaic pathogenic variants in *PORCN*. Males account for 10% of individuals with FDH; nearly all live-born affected males who have had molecular testing are mosaic for a *PORCN* pathogenic variant [Lombardi et al 2011]. It is presumed that non-mosaic, hemizygous males are not viable.

Risk to Family Members

Parents of a proband

- Approximately 95% of females with FDH have a *de novo* pathogenic variant.
- Approximately 5% of affected females have inherited a *PORCN* pathogenic variant from a parent, usually the mother; such women may be more, equally, or less affected than their mothers [Wang et al 2007, Shimaoka et al 2009].
    - Less frequently, an affected female may have inherited the pathogenic variant from a father mosaic for a *PORCN* pathogenic variant [Wang et al 2007]; fathers with FDH are typically more mildly affected than their daughters [Burgdorf et al 1981].
- **Female proband.** An apparently negative family history cannot be confirmed until appropriate evaluations have been performed.
    - If the *PORCN* pathogenic variant has been identified in a female proband, molecular genetic testing of the parent who has manifestations of FDH is appropriate.
    - If neither parent has clinical manifestations of FDH, molecular genetic testing of both parents should be considered because: (1) the father or mother may have low-level mosaicism or (2) the mother may be a mildly affected heterozygote secondary to extremely favorable skewing of X-chromosome inactivation.

- **Male proband.** Live-born affected males are rare and nearly always have somatic mosaicism for a *de novo*, presumably postzygotic pathogenic variant. The mother of a severely affected male should be examined for subtle features of FDH. Maternal testing is indicated as two hemizygous males have been reported as offspring of a seemingly asymptomatic mother with a presumed hypomorphic pathogenic variant and favorable skewing of X-chromosome inactivation [Brady et al 2015].

Sibs of a proband

- **Female proband.** The risk to sibs of a female proband depends on the genetic status of the mother and father:
  - If the **mother** is affected and/or heterozygous for the *PORCN* pathogenic variant, the risk at conception of a sib inheriting the variant is 50%. However, the risk at delivery that a sib will be affected is lower than 50% because nearly all male conceptuses with the variant are presumed to be spontaneously aborted. The expected ratio in live-born sibs is 33% unaffected females, 33% affected females, and 33% unaffected males.
  - If the **father** has the *PORCN* pathogenic variant, the risk to female sibs of inheriting the variant at conception is as high as 100% depending on the level of mosaicism in the father's germline. Male sibs are not at risk of inheriting the pathogenic variant from their father.
- **Male proband.** Because evidence from both molecular studies and clinical reports indicates that nearly all live-born males are mosaic for a postzygotic pathogenic variant, the risk to the sib of an affected male is similar to the population risk for this disorder.

Offspring of proband

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

Other family members. If the mother of the proband also has a *PORCN* pathogenic variant, her female family members may also be at risk of having the pathogenic variant (asymptomatic or symptomatic) and her father may be at risk of being mosaic for the pathogenic variant.

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 affected individuals.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *PORCN* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for FDH are possible.

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**
  108 Charlton Lane
  Cheltenham Gloucestershire GL53 9EA
  United Kingdom
  Phone: 01242 261332
  Email: diana@ectodermaldysplasia.org
  www.ectodermaldysplasia.org
- **National Foundation for Ectodermal Dysplasias (NFED)**
  410 East Main Street
  PO Box 114
  Mascoutah IL 62258-0114
  Phone: 618-566-2020
  Fax: 618-566-4718
  Email: info@nfed.org
  www.nfed.org
- **Ectodermal Dysplasias International Registry**
  National Foundation for Ectodermal Dysplasias
  410 East Main Street
  Mascoutah IL 62258
  Phone: 618-566-2020
  Fax: 618-566-4718
  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. Focal Dermal Hypoplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PORCN	Xp11.23	Protein-serine O-palmitoleoyltransferase porcupine	PORCN @ LOVD	PORCN	PORCN

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 Focal Dermal Hypoplasia (View All in OMIM)

300651	PORCUPINE O-ACYLTRANSFERASE; PORCN
305600	FOCAL DERMAL HYPOPLASIA; FDH

Gene structure. *PORCN* has 15 exons, 14 of which are coding exons. It undergoes alternative splicing, resulting in five transcript variants. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Pathogenic variants in *PORCN* include nonsense, frameshift, and missense variants as well as partial- and whole-gene deletions. Deletions may include flanking genes; however, no additional clinical features were reported [Grzeschik et al 2007, Wang et al 2007]. Nearly all affected males to date have somatic mosaicism for a *PORCN* pathogenic variant [Grzeschik et al 2007, Wang et al 2007, Lombardi et al 2011].

Normal gene product. *PORCN* encodes the human homolog of *Drosophila* porcupine [Caricasole et al 2002]. The gene product, human protein-serine O-palmitoleoyltransferase porcupine, has five isoforms that result from alternative splicing and is expressed in a wide variety of tissues.

In model organisms, porcupine has been shown to be required for secretion and signaling of most WNT proteins from WNT-producing cells [van Amerongen & Nusse 2009, Chen et al 2012, Clevers & Nusse 2012] and may play a role in fine-tuning WNT protein levels. WNT signaling is required for induction, proliferation, morphogenesis, and maintenance of most organs. WNTs are important secreted morphogens that interact with receptors and co-receptors on target cells. Activation of the WNT pathway is important for normal development [Clevers & Nusse 2012] and may be required to activate additional non-canonical Wnt signaling [Proffitt & Virshup 2012]. Wnt-3a is retained in the endoplasmic reticulum of cultured cells when *Porcn* is inactivated [Takada et al 2006, Clevers & Nusse 2012].

Abnormal gene product. Focal dermal hypoplasia is caused by loss-of-function pathogenic variants and deletions of *PORCN*.

Loss of function of 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]. Inactivation of *Porcn* in mouse embryos has resulted in early embryonic lethality and revealed that it is required for gastrulation and normal development of mesoderm and ectoderm-derived structures [Barrott et al 2011, Biechele et al 2011, Liu et al 2012]. Conditional inactivation of *Porcn* in developing skin causes alopecia because hair follicles do not form [Liu et al 2012], and in developing limbs causes skeletal defects reminiscent of those seen in persons with FDH [Barrott et al 2011, Liu et al 2012].

The new mouse models will be helpful in the future to further understand the normal function of porcupine and to test potential new therapies for those symptoms that are progressive or first present after birth.

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Chapter Notes

Author Notes

Dr. Sutton's website

Dr. Van den Veyver's website

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